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(54) Title: OPTICALLY ACTIVE PHOSPHITES AND PHOSPHORAMIDES BEARING BIPHENOL SKELETONS WITH AXIAL CHIRALITY, AND THEIR USE IN CATALYTIC ASYMMETRIC REACTIONS

(57) Abstract: Novel optically active ligands which are mondentate phosphites and phosphoramidites, and bidentate phosphites and phosphoramidites; optically active catalysts comprising a reaction mixture of the ligand and a transition metal or its compounds; and processes of using the optically active catalysts to produce optically active compounds.

TITLE

OPTICALLY ACTIVE PHOSPHITES AND PHOSPHORAMIDITES BEARING BIPHENOL SKELETONS WITH AXIAL CHIRALITY, AND THEIR USE IN CATALYTIC ASYMMETRIC REACTIONS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to novel optically active phosphite ligands and/or optically active phosphoramidite ligands, which are essential elements for catalytic asymmetric reactions.

Further, the invention relates to optically active catalysts comprising a transition metal or its compound and the foregoing novel optically active phosphite ligands and/or optically active phosphoramidite ligands, which are important for catalytic asymmetric reactions.

Moreover, the invention relates to processes of producing optically active compounds by catalytic asymmetric reactions of prochiral compounds using the foregoing optically active catalysts.

DESCRIPTION OF THE RELATED ART

Processes of producing optically active compounds by catalytic asymmetric reaction of prochiral compounds using a catalyst comprising a combination of a transition metal or its compound and an optically active ligand are well known. Such a reaction is characterized by the use of an optically active ligand. Such optically active ligands include optically active phosphines, optically active phosphine-phosphites, optically active phosphites, and optically active phosphoramidites. Among these compounds, the optically active phosphites comprise monodentate and bidentate phosphite compounds.

As the optically active monodentate phosphites, are known phosphites and/or phosphoramidites in which the moiety corresponding to Y of the general formula (1) in the phosphite having a biphenol skeleton is optically active (see WO 01/94278). However, these known phosphites and/or phosphoramidites do not have biphenol skeletons with axial chirality. Moreover, in accordance with the asymmetric hydrogenation reactions using the optically active phosphites as disclosed in WO 01/94278, the enantioselectivity achieved is 30% ee at the maximum.

As the bidentate phosphites, are known optically active bidentate phosphites with axial chirality. In these phosphites, a binaphthol moiety has axial chirality, but few optically active ligands in which a biphenol moiety has axial chirality are known. For example, Briggs, et al. (see Chemical Communication, 2001, 2174) synthesized an optically active bidentate phosphite ligand from (R)-3,3'-di-tert-butyl-6,6'-dimethyl-1,1'-biphenyl-2,2'-diol and performed hydroformylation reaction of propene using a catalyst comprising a Rh complex with this optically active phosphite. Since any of linear and branched products from propene (n-butanal and 2-methypropanal, respectively) do not have any chiral center, no asymmetric hydroformylation reaction of a prochiral olefin has been investigated with this phosphite ligand.

Further, WO 02/40491 titled "Ortho Substituted Chiral Phosphines and Phosphinites and Their Use in Asymmetric Catalytic Reactions" discloses a structure of optically active bidentate phosphites bearing a biphenol moiety with axial chirality and discloses that the optically active bidentate phosphites can be used as ligands for various asymmetric reactions. However, the WO 02/40491 merely discloses the structure and utilization, and does not describe the production processes of the optically active bidentate phosphites and relevant examples thereof. In addition, WO 02/40491 does not clearly indicate the efficacy of those ligands when they were used for the specific reactions.

Optically active phosphoramidites and asymmetric hydrogenation reactions using Ru or Rh catalysts with these phosphoramidite ligands are known (see WO 02/4466 and J. Am. Chem. Soc., 2000, 122, 11539). The phosphoramidites that are disclosed in this paper are based on the optically active binaphthol, which has axial chirality. However, there are no examples using phosphoramidites having an optically active biphenol skeleton with axial chirality.

As described above, optically active phosphites or phosphoramidites having an optically active binaphthol skeleton are hitherto known.

However, it has been shown that when these ligands are used for reactions at relatively high temperatures for a long period of time, the optical purity of these ligands gradually decreases because of racemization. Accordingly, there is an obvious limitation in the use of these ligands bearing the optically active binaphthol skeleton.

Although optically active biphenols with axial chirality are hitherto known, no example has been reported for the synthesis of optically active phosphites and/or phosphoramidites starting from these optically active biphenols with axial chirality.

An object of the present invention is to provide monodentate phosphites and/or phosphoramidites as well as bidentate phosphites and/or phosphoramidites having an optically active biphenol skeleton with axial chirality, which are structurally different from the known ligands and do not cause a substantial decrease in optical purity at high reaction temperatures.

Other objects of the invention are to provide novel optically active catalysts comprising a combination of such an optically active phosphite and/or phosphoramidite compound as a ligand and a transition metal or its compound in which the transition metal belongs to the groups 4 to 12 of the periodic table and to provide a process for producing optically active compounds using such novel optically active catalysts.

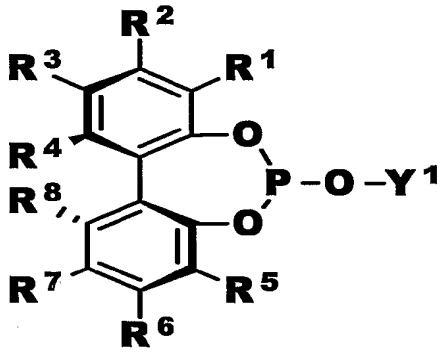
DETAILED DESCRIPTION OF THE INVENTION

The present inventors reasoned that if an optically active biphenol skeleton with axial chirality having substituents at the 6- and 6'-positions thereof is utilized, it is possible to provide an optically active phosphite or phosphoramidite that is not accompanied by racemization, or in which even when racemization occurs, the racemization process is extremely slow, even under forced conditions, and performed extensive and intensive investigations.

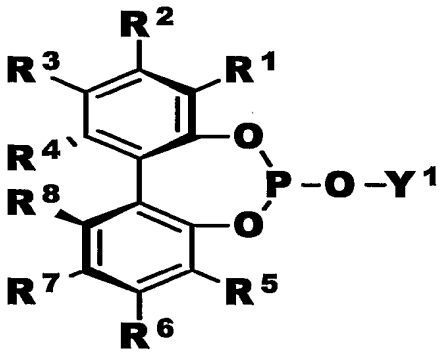
As a result, it has been found that a thermally stable chiral catalyst can be provided by combining an optically active phosphite and/or phosphoramidite having a specified substituent in a specified site of an optically active bisphenol skeleton with axial chirality as a ligand with a transition metal or its compound, in which the transition metal belongs to the groups 4 to 12 of the periodic table and that a process for giving an optically active compound with high optical purity can be provided by using this chiral catalyst, leading to the accomplishment of the invention.

Specifically, the invention according to one embodiment is concerned with a novel optically active monodentate phosphite and/or phosphoramidite bearing an optically active biphenol moiety with axial chirality, represented by the following general formula (1):

General Formula (1)



(1-1)



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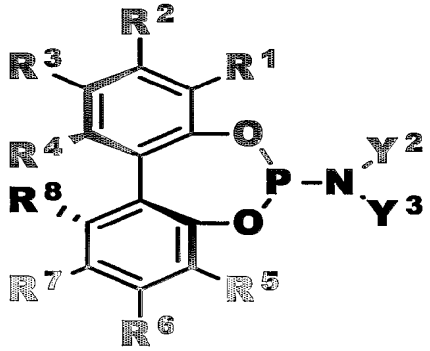
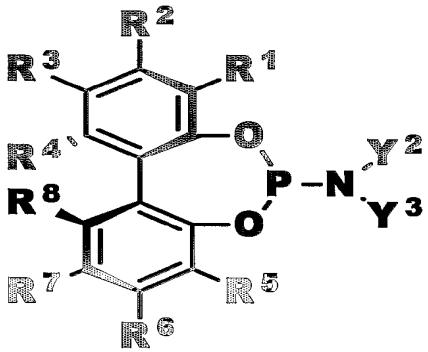


(1-3)



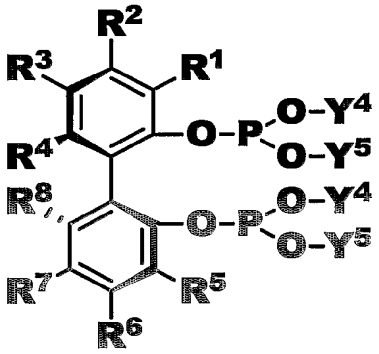
(1-4)

wherein R^1 and R^5 each represents a hydrogen atom or an optionally substituted secondary or tertiary hydrocarbon group having 3 to 20 carbon atoms; R^2 and R^6 each represents a hydrogen atom, an optionally substituted alkyl group having 1 to 20 carbon atoms, an optionally substituted alkoxy group having 1 to 10 carbon atoms, an optionally substituted aryl group, or a halogen atom; R^3 and R^7 each represents an optionally substituted hydrocarbon group having 1 to 20 carbon atoms or an optionally substituted alkoxy group having 1 to 10 carbon atoms; R^4 and R^8 each represents a hydrocarbon atom having 1 to 4 carbon atoms, a halogen atom, or an alkoxy group having 1 to 4 carbon atoms; Y^1, Y^2, and Y^3 each represents an optionally substituted alkyl group, an optionally substituted aryl group, or

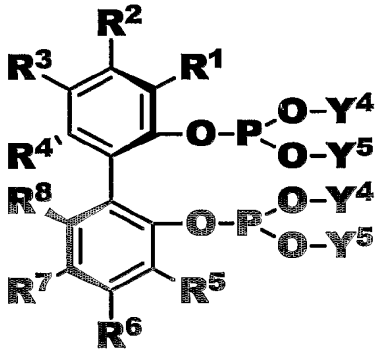
an optionally substituted heteroaryl group; and Y^2 and Y^3 may be taken together to form a ring.

The present invention according to another embodiment is concerned with a novel optically active bidentate phosphite and/or phosphoramidite bearing an optically active biphenol moiety with axial chirality, represented by the following general formula (2):

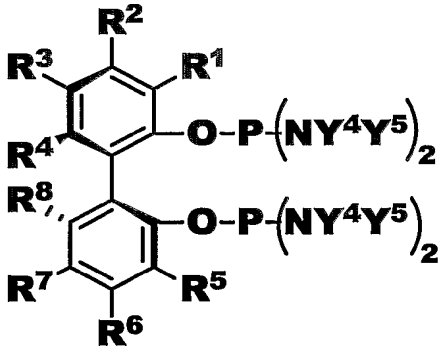
General Formula (2)



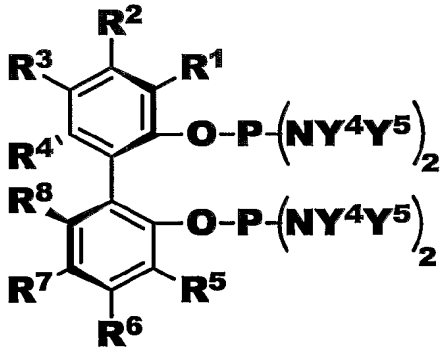
(2-1)



(2-2)



(2-3)



(2-4)

wherein R^1 and R^5 each represents a hydrogen atom or an optionally substituted secondary or tertiary hydrocarbon group having 3 to 20 carbon atoms; R^2 and R^6 each represents a hydrogen atom, an optionally substituted alkyl group having 1 to 20 carbon atoms, an

optionally substituted alkoxy group having 1 to 10 carbon atoms, an optionally substituted aryl group, or a halogen atom; R^3 and R^7 each represents an optionally substituted hydrocarbon group having 1 to 20 carbon atoms or an optionally substituted alkoxy group having 1 to 10 carbon atoms; R^4 and R^8 each represents a hydrocarbon atom having 1 to 4 carbon atoms, a halogen atom, or an alkoxy group having 1 to 4 carbon atoms; Y^4 and Y^5 each represents an optionally substituted alkyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group; and Y^4 and Y^5 may be taken together to form a ring.

In the present invention, according to still another embodiment, the novel optically active monodentate phosphite and/or phosphoramidite compound and/or the optically active bidentate phosphite and/or phosphoramidite compound provides a novel optically active catalyst upon reaction with a transition metal or its compound. The optically active catalyst of the invention is useful as a chiral source of optically active monomer compounds or optically active polymer compounds. Since the optically active catalysts of this invention comprise the foregoing novel optically active compounds as ligands, the optically active catalysts arising from these combinations are structurally different from the conventional ones.

Further, the present invention, according to still yet another embodiment, is concerned with a process of producing optically active compounds using the optically active catalysts described above, wherein various prochiral compounds are used as substrates, and the optically active catalysts are used as chiral sources.

PRODUCTION OF OPTICALLY ACTIVE PHOSPHITES AND PHOSPHORAMIDITES OF THE INVENTION

A. Novel optically active monodentate phosphites and/or phosphoramidites with axial chirality

A-1. Process for producing optically active biphenols

The present inventors already reported a patent regarding a production process for optically active biphenols (see Japanese Patent Application No. 2002-362327). A general synthetic process thereof is briefly described below with reference to 6,6'-dimethyl-1,1'-biphenyl-2,2'-diol derivatives.

A-1-(a) Process in which a precursor of an optically active 6,6'-dimethyl-1,1'-biphenyl-2,2'-diol derivative is prepared first and then converted to the desired optically active biphenols:

A-1-(a)-(1) A process in which a phenol compound having an optically active substituent is subjected to asymmetric Grignard coupling to synthesize an optically active biphenyl skeleton, and the substituent is then converted to a methyl group through several steps (see Moorlag, Henk; Meyers, A.I., *Tetrahedron Lett.*, 1993, 34(44), 6993-6).

A-1-(a)-(2) A process in which an optically active biphenyl skeleton is synthesized by diether formation of a biphenyl tetraol compound with an optically active diol and subjected to alkylation reaction with an organo-zinc reagent to give the corresponding optically active biphenol (see Tuyet, Tran Mai Thi; Harada, Toshio; Hashimoto, Kazuyuki; Hatsuda, Masanori; Oku, Akira, *J. Org. Chem.*, (2000), 65(5), 1335-1343).

However, these processes in which a chiral biphenyl skeleton is synthesized and then converted to the desired optically active biphenols include many steps and require complicated operation.

A-1-(b) Process of separating optically active biphenols from racemic of a 6,6'-dimethyl-1,1'-biphenyl-2,2'-diol derivative:

A-1-(b)-(1) A process of separating a racemic biphenol to the corresponding optically active biphenol by chromatography:

For example, there is a known process in which the chromatographic separation is achieved by using an optically active column (see Kaida, Yuriko; Okamoto, Yoshio, *Bull. Chem. Soc. Jpn.*, (1993), 66(8), 2225-32).

However, this process is not suitable for mass production for reasons such as necessity of a large amount of solvent.

A-1-(b)-(2) A process in which a racemic biphenol is derived into a mixture of diastereomers, followed by separation:

A-1-(b)-(2)-1) There is a known process in which a diastereomeric clathrate compound is selectively formed by using an optically active amine derivative, followed by separation of the diastereomers (see JP-A-10-45648).

With respect to this process, not only the optically active amine derivative to be used is expensive, but also this process can separate only one of the two enantiomers at a time. In order to obtain both enantiomers of the biphenol, it is necessary to form a clathrate compound again with an amine with the opposite absolute configuration.

A-1-(b)-(2)-2) There is a known process in which a racemic biphenol is converted to a phosphoric acid diester, which then forms a salt with an optically active amine and the resulting diastereomeric salts are separated (see Kanoh, Shigeyoshi; Tamura, Nobuyuki; Motoi, Masatoshi; Suda, Hiroshi, *Bull. Chem. Soc. Jpn.*, (1987), 60(6), 2307-9).

With respect to this process, it is possible to separate only one enantiomer of the desired biphenol at a time. In order to obtain both enantiomers, it is necessary to form a salt using the amine with the opposite absolute configuration.

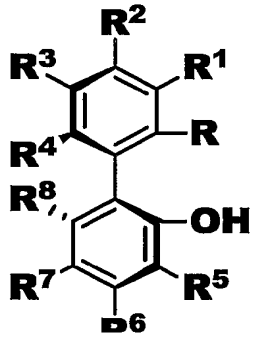
A-1-(b)-(2)-3) A process in which a phosphite having a phosphorus atom-containing cyclic structure, which is derived from a racemic biphenol, phosphorus trichloride and an optically active secondary alcohol, is (a) oxidized to give a phosphoric ester, which is then (b) optically resolved by recrystallization to yield an optically active compound, followed by (c) hydrogenation to afford an enantiomer of biphenol.

The racemic biphenols to be used for these processes can be synthesized through the oxidative coupling reaction of the corresponding phenols, which are readily available raw materials. There is also a known synthetic method not using the oxidative coupling (see Y. Sugii; H. Shindo, *Yakugaku Zasshi (Journal of the Pharmaceutical Society of Japan)*, 54, 829-844 (1934)). However, this method involves many steps and the yields of the desired biphenols are low.

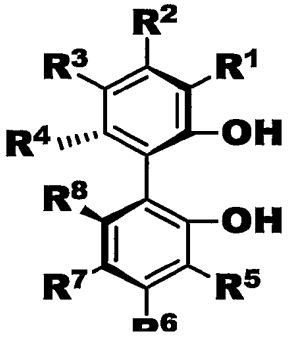
To obtain the optically active biphenol, the optical resolution method may be used, which has advantages such as the availability of the starting phenols and the easiness of the synthesis of racemic biphenols. From a practical point of view, the process A-1-(b)-(2)-3) is preferable because both enantiomers can be obtained by the single process without waste. However, this invention is not limited thereto.

The optically active biphenols represented by the following general formula (3) are produced according to the foregoing process.

General Formula 3



(3-1)



(3-2)

R^1 and/or R^5 represents a hydrogen atom or an optionally substituted secondary or tertiary hydrocarbon group having 3 to 20 carbon atoms.

When R^1 and/or R^5 represents a hydrogen atom, in the case where the resulting optically active phenol is used to prepare the corresponding optically active phosphite or phosphoramidite ligand, a high optical yield can be achieved. In the present invention, the optical yield as referred to herein is represented by the enantiomeric excess (% ee) of the optically active products obtained.

When R^1 or R^5 represents an optionally substituted secondary or tertiary hydrocarbon group having 3 to 20 carbon atoms, the resulting optically active phenol, when converted to the corresponding phosphite or phosphoramidite ligand, sterically or electronically influences the reaction system, whereby a good stability of the active catalyst species and a high optical yield can be achieved.

The number of carbon atoms of the substituted hydrocarbon group is preferably 10 or less, and more preferably 5 or less. In the present invention, the number of carbon atoms of the optionally substituted hydrocarbon group as referred to herein means the number of total carbon atoms of the hydrocarbon group and the substituent. Preferred examples of the hydrocarbon group include an isopropyl group, a tert-butyl group, and a tert-amyl group, with an isopropyl group and a tert-butyl group being more preferred.

Examples of the substituent include an alkoxy group, a carbalkoxy group, a dialkylamino group, a halogen atom, and a nitro group. The number of carbon atoms of the alkoxy group is usually 1 to 10; the number of carbon atoms of the carbalkoxy group is usually 2 to 10, and preferably 2 to 4; and the number of carbon atoms of the dialkylamino group is usually 2 to 10.

Though R^1s and R^5s may be different from each other, it is preferred that R^1s and/or R^5s are the same because the synthesis of these compounds is easy.

R^2 and R^6 each represents a hydrogen atom, an optionally substituted alkyl group having 1 to 20 carbon atoms, an optionally substituted alkoxy group having 1 to 10 carbon atoms, an optionally substituted aryl group, or a halogen atom.

The number of carbon atoms of the hydrocarbon group is preferably 1 to 10, and more preferably 1 to 5; and the number of carbon atoms of the alkoxy group is preferably 1 to 5. In the present invention, the number of carbon atoms of the optionally substituted alkoxy group as referred to herein means the number of total carbon atoms of the hydrocarbon group and the substituent.

Examples of the hydrocarbon group include an alkyl group, an aryl group, and an aralkyl group. Of these, an alkyl group is preferable because of the availability of the raw material. Among the substituents a methyl group, a methoxy group, a chlorine, and a fluorine are preferred. Though R^2s and/or R^6s may be different from each other, it is preferred that R^2s and/or R^6s are the same because the synthesis of these compounds is easy.

R^3 and R^7 each represents an optionally substituted hydrocarbon group having 1 to 20 carbon atoms or an optionally substituted alkoxy group having 1 to 10 carbon atoms. When R^3 or R^7 has the foregoing substituent, the thermal stability of the biphenol increases, and a higher selectivity in the desired catalytic asymmetric reactions can be realized. As a result, a high optical yield can be achieved.

The number of carbon atoms of the hydrocarbon group is preferably 1 to 10, and more preferably 1 to 5; and the number of carbon atoms of the alkoxy group is preferably 1 to 5. In the present invention, the number of carbon atoms of the optionally substituted alkoxy group as referred to herein means the number of total carbon atoms of the hydrocarbon group and the substituent.

A hydrocarbon group has preferably 1 to 5 carbon atoms, with a methyl group, an ethyl group, an isopropyl group, a t-butyl group, and a t-amyl group being more preferred.

R^4 and R^8 each represents a hydrocarbon atom having 1 to 4 carbon atoms, a halogen atom, or an alkoxy group having 1 to 4 carbon atoms. Among these, a methyl group is the most preferable.

The optically active biphenols thus produced will serve as the starting materials for the production of the optically active monodentate phosphites and/or phosphoramidites as well as optically active bidentate phosphites and/or phosphoramidites.

A-2 Process for producing optically active phosphites and/or phosphoramidites

A-2-(a) Process for the production of monodentate phosphite and/or phosphoramidite

The optically active monodentate phosphite can be produced essentially in the same manner as that for the production of the racemic monodentate phosphite. For example, it can be produced by the method as described in JP-T-61-501268. The detailed production process is described below.

A-2-(a)-(1) The optically active monodentate phosphites and/or phosphoramidites can be synthesized by reacting phosphorus trichloride with an alcoholic hydroxyl group-containing compound or phenolic hydroxyl group-containing compound represented by the following general formula (4-1):

Y^1-OH (4-1)

wherein Y^1 represents an optionally substituted alkyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group, or

an amine represented by the following general formula (4-2):

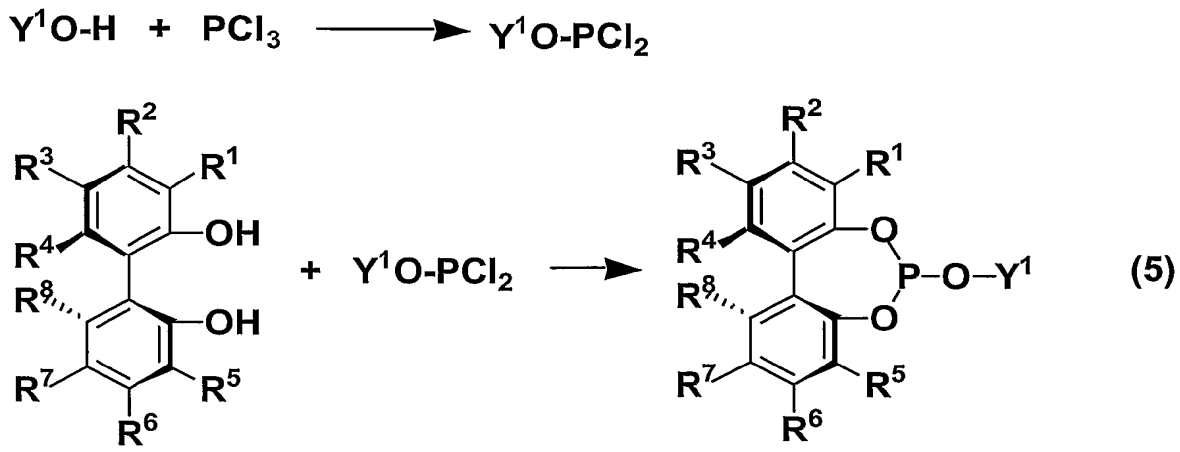
Y^2Y^3-NH (4-2)

wherein Y^2 and Y^3 each represents an optionally substituted alkyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group; and Y^2 and Y^3 may be taken together to form a ring,

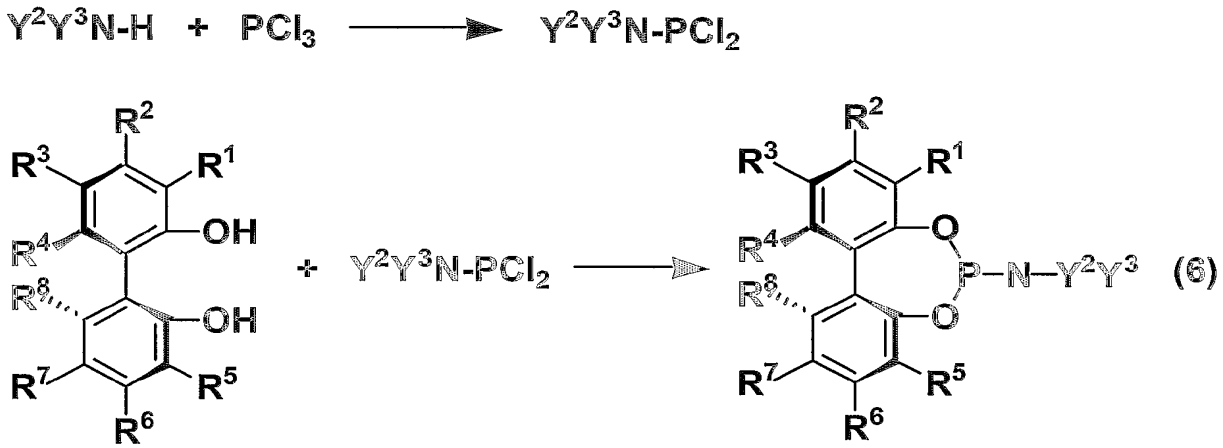
in the presence or absence of a base, to prepare a dichlorophosphite and further reacting the dichlorophosphite with an optically active biphenol represented by the foregoing general formula (4) in the presence or absence of a base.

The synthetic routes are illustrated in the following scheme (5) (for phosphites) and scheme (6) (for phosphoramidites), respectively.

(a-1: Phosphites)



(a-1: Phosphoramidites)



Y^1 represents an alkyl group, an aryl group, or a heteroaryl group, each of which may have a substituent having 1 to 20 carbon atoms.

The number of carbon atoms of the alkyl group is preferably 1 to 30, and more preferably 1 to 20. The alkyl group may be an optically active group in which the substituent has a chiral center. Examples of the alkyl group include linear and branched alkyl groups such as a methyl group, an ethyl group, a propyl group, a t-butyl group, an octyl group, and a dodecyl group; cycloalkyl groups such as a cyclopropyl group, a cyclobutyl group, a cyclohexyl group, a cyclooctyl group, an optically active 2-phenyl-1-cyclohexyl group, and

an optically active menthyl group; and aralkyl groups such as a benzyl group, an optically active 1-phenylethyl group, and a 4-phenylbutyl group.

The number of carbon atoms of the aryl group is preferably 6 to 30, and more preferably 6 to 20. The aryl group may be an optically active group in which the substituent has a chiral center. Specific examples of the aryl group include a phenyl group, an α-naphthyl group, a β-naphthyl group, an anthranyl group, a 4-(optically active 2-butyl)-phenyl group, an o-tolyl group, a p-tolyl group, a 2,4-di-t-butylphenyl group, a p-methoxyphenyl group, an m-fluorophenyl group, and a 3-t-butyl-2-naphthyl group. The heteroaryl group may be an optically active group in which the substituent has a chiral center. Specific examples of the heteroaryl group include a 2-pyridyl group, a 3-pyridyl group, a 4-pyridyl group, a 4-(optically active 2-butyl)-pyridyl group, a 3-furyl group, a 2-furyl group, and a 2,5-dimethyl-3-pyrrolyl group.

Y^2 and Y^3 are synonymous with Y^1. In the case where Y^2 and Y^3 are taken together to form a ring, examples of the ring include an alkylene group and an arylene group, each of which may have a substituent having 1 to 20 carbon atoms.

The number of carbon atoms of the alkylene group is preferably 2 to 20, and more preferably 2 to 10. Specific examples of the alkylene group include a 1,2-ethylene group, an optically active 2-methyl-1,2-ethylene group, a 1,3-propylene group, a 1,4-butylene group, an optically active 2-methyl-1,4-butylene group, a 3-isopropyl-1,5-pentylene group, and a 2-chloro-1,4-butylene group. The number of carbon atoms of the arylene group is preferably 6 to 20, and more preferably 6 to 16. Specific examples of the arylene group include a 2,2'-biphenylene group, a 1,1'-binaphthylene group, a 4,4'-dimethyl-2,2'-biphenylene group, an optically active 1,1'-binaphtylene group, and an optically active 3,3'-dibromobinaphthylene group.

A-2-(a)-(2) The optically active monodentate phosphites and/or phosphoramidites can also be synthesized by reacting phosphorus trichloride with an optically active biphenol represented by the foregoing general formula (3) to prepare an optically active cyclic monochlorophosphite compound and further reacting the optically active cyclic monochlorophosphite compound with an alcoholic hydroxyl group-containing compound or a phenolic hydroxyl group-containing compound represented by the following general formula (4-1):

$$Y^1\text{-OH} \qquad (4\text{-}1)$$

wherein Y^1 is the same as defined above, or

an amine represented by the following general formula (4-2):

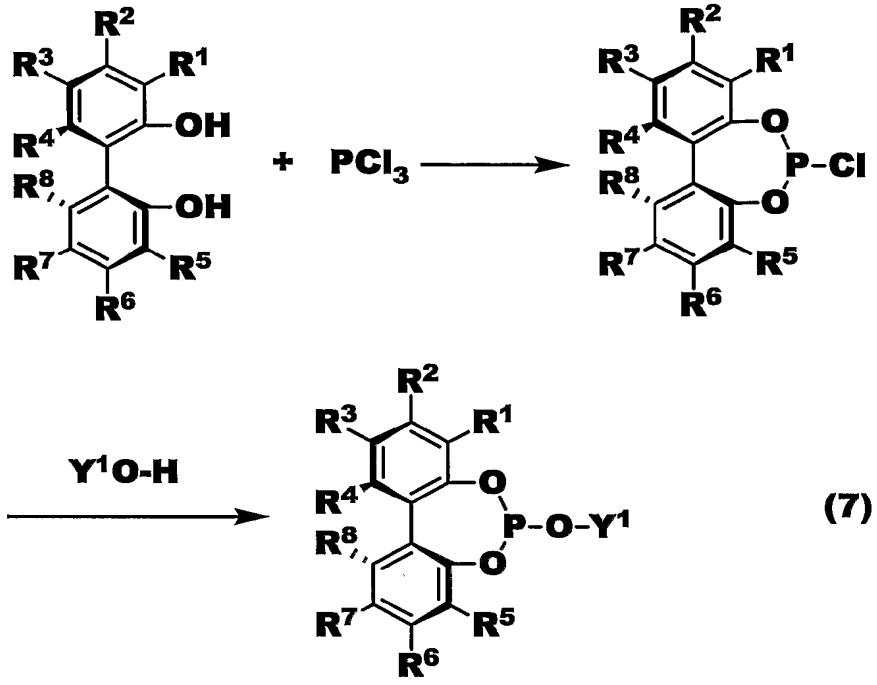
$$Y^2Y^3\text{-}NH \qquad (4\text{-}2)$$

wherein Y^2 and Y^3 are the same as defined above,

in the presence or absence of a base.

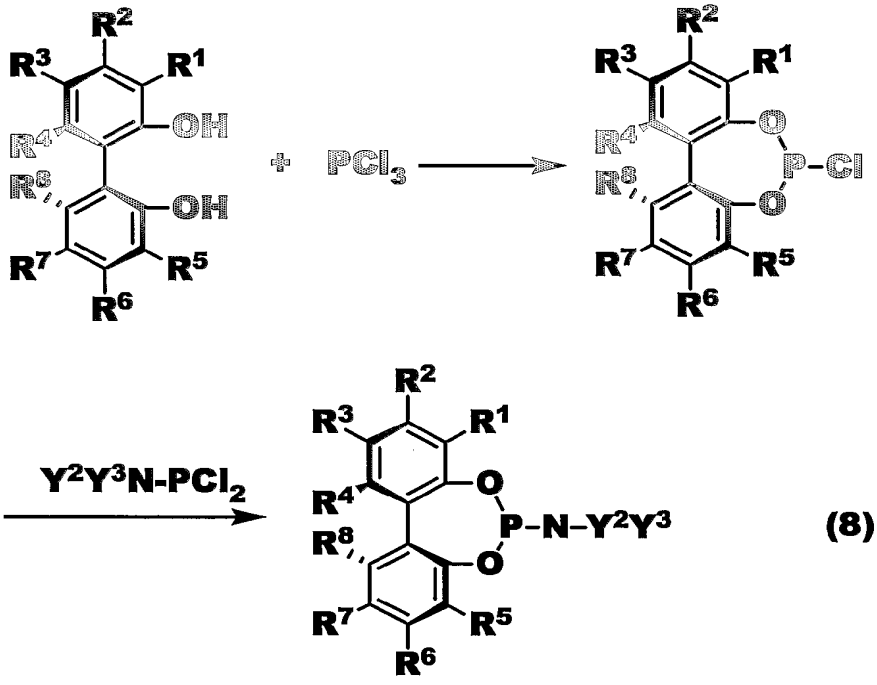
The synthetic routes are illustrated in the following scheme (7) (for phosphites) and scheme (8) (for phosphoramidites), respectively.

(a-2: Phosphites)



(7)

(a-2: Phosphoramidites)



(8)

The method to be used varies depending on the structure of the compound (3). In the case of a compound having bulky tertiary substituents such as a tertiary butyl group as R^1 and R^5, the method via the dichlorophosphite compound shown in A-2-(a)-(1) is preferred. However, the method via an optically active cyclic monochlorophosphite is advantageous in producing various derivatives because this compound can serve as an intermediate for the synthesis of optically active phosphoramidite compounds as described later.

Next, the reaction conditions of the method A-2-(a)-(1), i.e., the preparation of the dichlorophosphite, is described below in detail.

The reaction conditions for the preparation of the dichlorophosphite are not particularly limited, and known methods can be employed.

In this reaction, in order to suppress the formation of a monochlorophosphite as a by-product, it is desirable that the reaction is carried out by using an excess of phosphorus trichloride and that the excessive phosphorus trichloride is removed by distillation after the reaction.

If a base is added for the purpose of capturing hydrogen chloride generated, the formation of the monochlorophosphite is increased. Accordingly, the addition of a base is not desirable.

Next, the preparation of a monochlorophosphite having a cyclic structure shown in A-2-(a)-(2) is described below.

The cyclic monochlorophosphite can be prepared by reacting the optically active biphenol represented by the general formula (4) with phosphorus trichloride in the presence of a base.

Examples of the solvent that can be used in the reaction include hydrocarbon solvents such as toluene and heptane; ether-based solvents such as THF (tetrahydrofuran) and dioxane; and aprotic polar solvents such as DMF (dimethylformamide) and DMSO (dimethyl sulfoxide). Among these solvents are preferable hydrocarbon solvents and ether-based solvents, with toluene and THF being particularly preferred.

Examples of the base include amine bases such as triethylamine and pyridine; and inorganic bases such as potassium carbonate, sodium hydroxide, and metal alkoxides (e.g., sodium methoxide). Among these bases, amine bases are preferable. This is because when the amine base is used, the amine base reacts with hydrogen chloride formed as a by-product along with the progress of the reaction to give an amine hydrochloride. The amine hydrochloride can be easily removed because of its low solubility in the solvent.

The amount of the base to be used is usually two molar equivalents or more to the optically active biphenol. From an economical point of view, the amount of the base to be used is preferably selected from the range of two molar equivalents to three molar equivalents.

The reaction temperature is not particularly limited, but is usually selected from the range of –100 °C to the reflux temperature of the solvent. Preferably, the reaction temperature is properly selected from the range of –78 °C to 80 °C.

Since phosphorus trichloride is used in the reaction, the reaction is preferably carried out under an atmosphere of an inert gas such as nitrogen.

The reaction time is not particularly limited, but is usually selected from the range of 1 minute to 48 hours, preferably from 5 minutes to 36 hours, and more preferably from 10 minutes to 24 hours.

After completion of the reaction, for example, the amine hydrochloride formed as a by-product is filtered off preferably under a nitrogen atmosphere, and the filtrate can be used for the subsequent reaction as it is.

The optically active cyclic monochlorophosphite, thus prepared, is reacted with an alcoholic hydroxyl group-containing compound or a phenolic hydroxyl group-containing compound represented by the general formula (4-1), Y^1-OH or an amine represented by the general formula (4-2), Y^2Y^3N-H in a solvent in the presence of a base, whereby the optically active monodentate phosphite and/or phosphoramidite represented by the general formula (1), can be produced.

Examples of the solvent that can be used in the reaction include hydrocarbon solvents such as toluene and heptane; ether-based solvents such as THF and dioxane; and aprotic polar solvents such as DMF and DMSO. Among these reaction solvents are preferable hydrocarbon solvents and ether-based solvents, with toluene and THF being particularly preferred.

Examples of the base include amine bases such as triethylamine and pyridine; and inorganic bases such as potassium carbonate, sodium hydroxide, and metal alkoxides (e.g., sodium methoxide). Among these bases, amine bases are preferable. This is because when the amine base is used, the amine base reacts with hydrogen chloride formed as a by-product along with the progress of the reaction to give an amine hydrochloride. The amine hydrochloride can be easily removed because of its low solubility in the solvent.

The amount of the base to be used is usually one molar equivalent or more to the optically active cyclic monochlorophosphite. From an economical point of view, the amount of the base to be used is preferably selected from the range of one molar equivalent to four molar equivalents.

The reaction temperature is not particularly limited, but is usually selected from the range of −100 °C to the reflux temperature of the solvent. Preferably, the reaction temperature is properly selected from the range of −78 °C to 80 °C.

Since phosphorus trichloride is used in the reaction, the reaction is preferably carried out under an atmosphere of an inert gas such as nitrogen.

The reaction time is not particularly limited, but is usually selected from the range of 1 minute to 48 hours, preferably from 5 minutes to 36 hours, and more preferably from 10 minutes to 24 hours.

After completion of the reaction, for example, the amine hydrochloride formed as a by-product is filtered off preferably under a nitrogen atmosphere, and the desired compound is obtained through a purification step.

As the method of purifying the optically active monodentate phosphite and/or phosphoramidite compound, thus obtained, column chromatography suspension and rinsing, and/or recrystallization can be used.

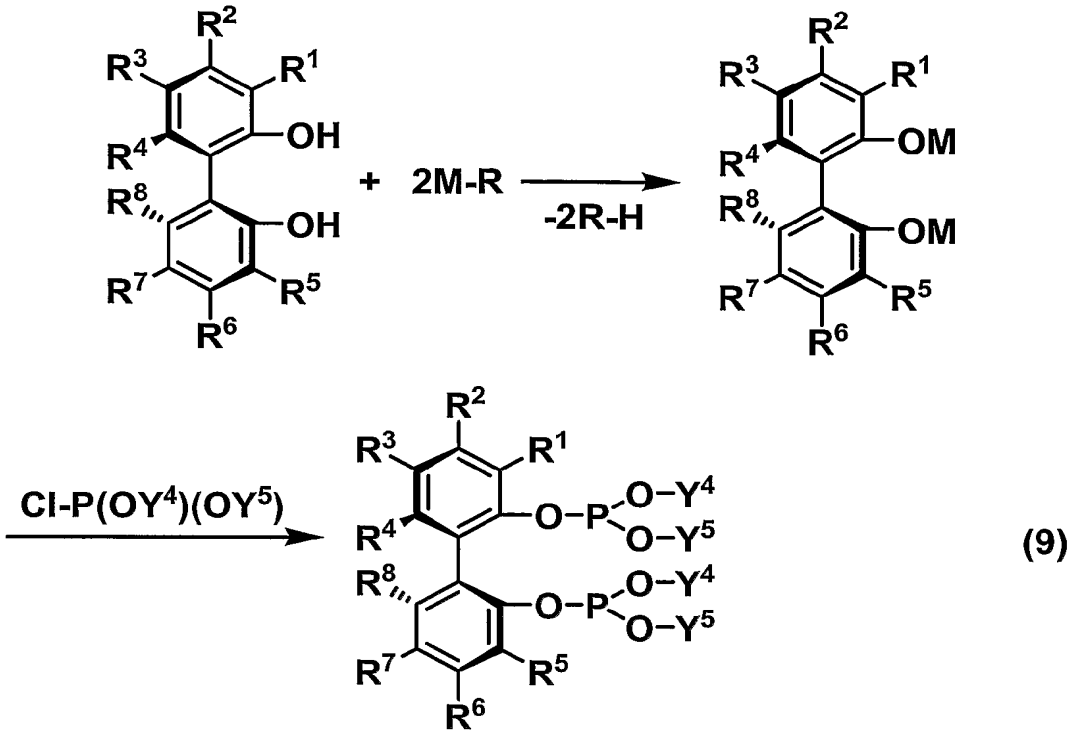
A-2-(b) Process for production of optically active bidentate phosphites and/or phosphoramidites

The production process for the bidentate phosphites and/or phosphoramidites slightly varies depending upon the structure of the compound, but is not particularly limited. The bidentate phosphites and/or phosphoramidites can be produced according to the known literature methods for producing the following racemic bidentate phosphite. Examples of the known literature methods are described in JP-A-62-116587, JP-A-10-45775, JP-A-2000-53688, and Japanese Patent Application No. 2000-228821.

A-2-(b)-(1) Bidentate phosphites and/or phosphoramidites where Y^4 and Y^5 are not taken together in the general formula (2):

Examples of the known literature methods are described in JP-A-10-45775, JP-A-2000-53688, and Japanese Patent Application No. 2000-228821.

The synthetic route is illustrated in the following scheme (9).



(9)

The optically active biphenol represented by the general formula (4) is reacted with an alkali metal compound such as NaH, KH, n-BuLi, and Na or an alkaline earth metal compound such as methylmagnesium bromide and ethylmagnesium bromide in a solvent preferably under an atmosphere of an inert gas such as nitrogen, to prepare the corresponding alkali metal salt or alkaline earth metal salt of the optically active biphenol.

With respect to the amount of the alkali metal compound or alkaline earth metal compound to be used, two moles per mole of the biphenol are usually sufficient. If necessary, the alkali metal compound or alkaline earth metal compound may be used in an amount more than two moles per mole of the biphenol.

Examples of the solvent that is suitably used include ethers such as THF and diethyl ether; hydrocarbons such as hexane and toluene; nitrogen-containing compounds such as pyridine, triethylamine, and N,N,N',N'-tetramethyl-ethylenediamine; and mixtures thereof.

The reaction temperature can be properly selected from the range of –70 °C to the boiling point of the solvent. It is also possible to start the reaction at a temperature in the range of –70 °C to 0 °C and then continue to gradually elevate the temperature to the boiling point of the solvent.

From a practical view of the reaction operation, it is preferred to perform the reaction by using NaH or n-BuLi as the metal compound and THF as the solvent.

The reaction time is usually in the range of 1 minute to 48 hours, and preferably 10 minutes to 4 hours.

After completion of the reaction, the reaction mixture can be used for the subsequent step as it is. Accordingly, isolation and/or purification is not particularly required.

In the case where the isolation is desirable, the reaction solvent is distilled off from the resulting reaction mixture, and the residue is dried, whereby the alkali metal salt or alkaline earth metal salt of the optically active biphenol can be obtained as a solid. If desired, recrystallization may be performed.

Next, the resulting alkali metal salt or alkaline earth metal salt of the optically active biphenol is reacted with a chlorophosphite represented by the general formula, $(Y^4O)(Y^5O)PCl$ or a diaminochlorophosphine represented by the general formula, $(Y^4N)(Y^5N)PCl$, separately prepared, in the presence or absence of a solvent, whereby the desired optically active bidentate phosphite and/or phosphoramidite compound represented by the general formula (2) can be obtained.

The reaction is carried out by mixing the alkali metal salt or alkaline earth metal salt of the optically active biphenol with the chlorophosphite or the diaminochlorophosphine at a temperature of 20 °C or lower. Preferably, the reactants are mixed with each other at a temperature of 0 °C or lower, and the temperature is then gradually elevated.

It is preferred that the reaction is carried out under an atmosphere of an inert gas such as nitrogen.

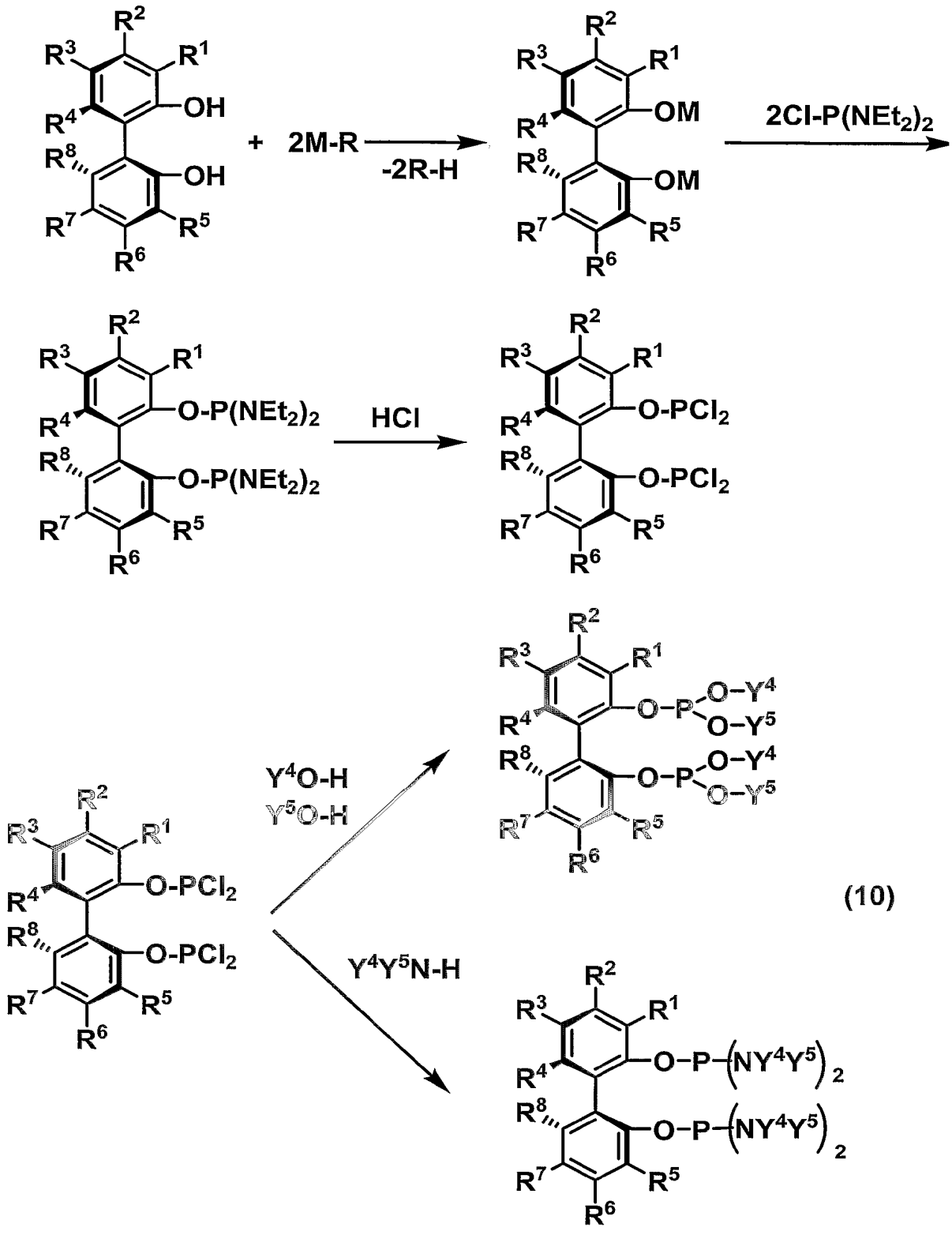
Examples of the solvent that can be used in the reaction include ethers such as THF, diethyl ether, and dioxane; hydrocarbons such as hexane and toluene; nitrogen-containing compounds such as pyridine and triethylamine; and mixtures thereof. With respect to the amount of the solvent, it is preferred to use a minimum amount of the solvent necessary for dissolving the reactants. The solvent may be used in an amount more than the minimum amount.

As the method of purifying the optically active bidentate phosphite and/or phosphoramidite, thus obtained, column chromatography, suspension and rinsing, and/or recrystallization can be used.

In the foregoing preparation method, there may be the case where a non-negligible amount of the monodentate phosphite and/or phosphoramidite represented by the general formula (1) is formed as a by-product.

To avoid the formation of this by-product, the alkali metal salt or alkaline earth metal salt of the optically active biphenol may be reacted with two equivalents of diethylaminophosphine, for example, to give the corresponding bidentate phosphoramidite. Then, the bidentate phosphoramidite is reacted with a hydrogen halide to yield the corresponding tetrahalobisphosphorus compound, which is reacted with a compound represented by the general formula, Y^4OH and/or Y^5OH or Y^4Y^5N-H, in the presence or absence of a base, to afford the optically active bidentate phosphite and/or phosphoramidite represented by the general formula (2).

The synthesis route is illustrated in the following scheme (10).



(10)

As the hydrogen halide, hydrogen chloride is preferable. In this case, a solution having hydrogen chloride dissolved therein may be used, or gaseous hydrogen chloride may be directly used.

In this reaction, the use of a solvent is not essential. If desired, however, the reaction can be carried out in an inert solvent. Preferred examples of the solvent to be used include hydrocarbons such as hexane, heptane, toluene, and xylene; ketones such as acetone, diethyl ketone, and methyl ethyl ketone; ethers such as THF, diethyl ether, and dioxane; and esters such as ethyl acetate.

In the present invention, the amount of the hydrogen halide to be used is not particularly limited, but is usually selected from the range of 0.01 to 1,000 molar equivalents, preferably from 0.1 to 100 molar equivalents, and particularly preferably from 2 to 4 molar equivalents with respect to the number of nitrogen atoms bound to the phosphorus atom.

The reaction temperature is selected from the range of –78 °C to 80 °C, preferably -50 °C to 50 °C, and particularly preferably –30 °C to 30 °C.

The tetrachlorobisphosphorus compound is reacted with the compound represented by the general formula, Y^4OH and/or Y^5OH or Y^4Y^5N-H, in a solvent preferably in the presence of a base, the optically active bidentate phosphite and/or phosphoramidite compound can be prepared.

Examples of the solvent that can be used in the reaction include hydrocarbon solvents such as toluene and heptane; ether-based solvents such as THF and dioxane; and aprotic polar solvents such as DMF and DMSO. Among these solvents are preferable hydrocarbon solvents and ether-based solvents. Especially, toluene and THF are preferred.

Examples of the base include amine bases such as triethylamine and pyridine; and inorganic bases such as potassium carbonate, potassium hydroxide, and metal alkoxides (e.g., sodium methoxide). Among these bases, amine bases are preferable. This is because when the amine base is used, the amine base reacts with hydrogen chloride formed as a by-product along with the progress of the reaction to give an amine hydrochloride. The amine hydrochloride can be easily removed because of its low solubility in the solvent. The amount of the base to be used is usually four molar equivalents or more to the tetrachlorobisphosphorus compound. From an economical point of view, the amount of the base to be used is preferably selected from the range of four molar equivalents to eight molar equivalents.

The reaction temperature is not particularly limited, but is usually selected from the range of −100 °C to the reflux temperature of the solvent. Preferably, the reaction temperature is properly selected from the range of −78 °C to 80 °C.

Since a polyhalogenated bisphosphorus compound is used in the reaction, the reaction is preferably carried out under an atmosphere of an inert gas such as nitrogen.

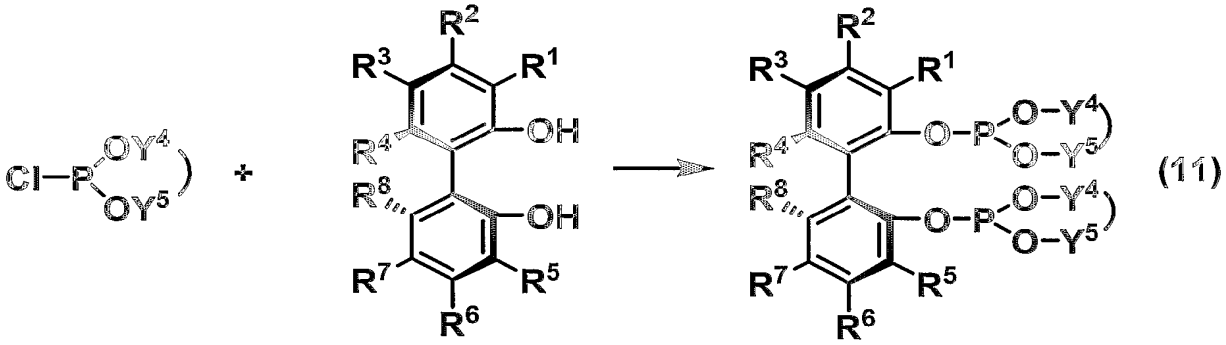
The reaction time is not particularly limited, but is usually selected from the range of 1 minute to 48 hours, preferably 5 minutes to 36 hours, and more preferably 10 minutes to 24 hours.

After completion of the reaction, for example, the amine hydrochloride formed as a by-product is filtered off preferably under a nitrogen atmosphere, and the desired compound is obtained through a standard purification procedure.

As the method of purifying the optically active bidentate phosphite and/or phosphoramidite, thus, obtained, column chromatography, suspension and rinsing, and/or recrystallization can be used.

A-2-(b)-(2) Bidentate phosphates where Y^4 and Y^5 are taken together to form a ring in the general formula (2):

The synthetic route is illustrated in the following scheme (11).



(11)

In the case where Y^4 and Y^5 are taken together to form a ring, the compound has two hydroxyl groups within the same molecule, for example, a diol compound. A diol is reacted with PCl_3 to give the corresponding cyclic chlorophosphite. The resulting cyclic chlorophosphite is reacted with the optically active biphenol in a solvent in the presence of a base, whereby the bidentate phosphite can be prepared.

The reaction is carried out at a temperature in the range of −78 °C to 100 °C, preferably −50 °C to 80 °C, and more preferably −30 °C to 70 °C.

The reaction is preferably carried out under an atmosphere of an inert gas such as nitrogen. Examples of the solvent that can be used in the reaction include ethers such as

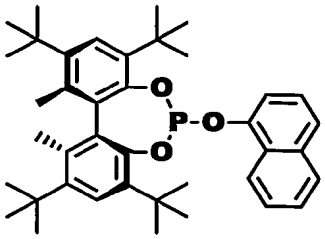
THF, diethyl ether, and dioxane; hydrocarbons such as hexane and toluene; nitrogen-containing compounds such as pyridine and triethylamine; and mixtures thereof. With respect to the amount of the solvent, it is preferred to use the minimum amount of the solvent necessary for dissolving the reactants. The solvent may be used in an amount more than the minimum amount.

Examples of the base include amine bases such as triethylamine and pyridine; and inorganic bases such as potassium carbonate, sodium hydroxide, and metal alkoxides (e.g., sodium methoxide). Among these bases, amine bases are preferable. This is because when the amine base is used, the amine base reacts with hydrogen chloride formed as a by-product along with the progress of the reaction to give an amine hydrochloride. The amine hydrochloride can be easily removed because of its low solubility in the solvent. The amount of the base to be used is usually two molar equivalents or more to the optically active biphenol. From an economical point of view, the amount of the base to be used is preferably selected from the range of two molar equivalents to four molar equivalents.

As the method of purifying the optically active bidentate phosphites and/or phosphoramidites, thus obtained, column chromatography, suspension and rinsing, and/or recrystallization can be used.

The optically active phosphites and/or phosphoramidites according to the present invention are exemplified by the following structures.

Monodentate phosphite and/or phosphoramidite compounds:



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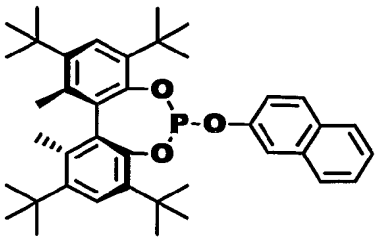

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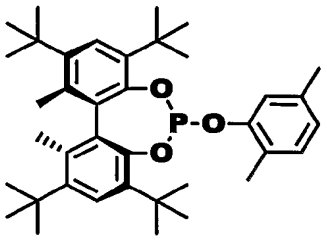

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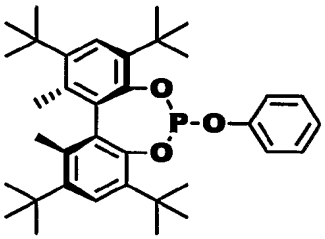

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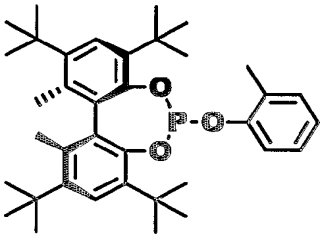

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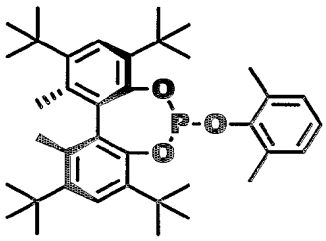

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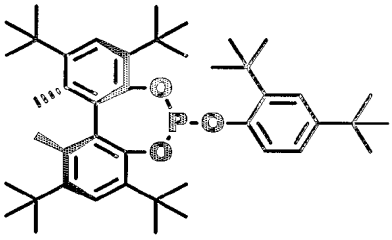

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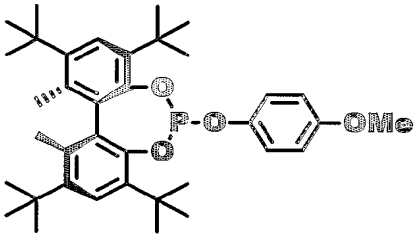

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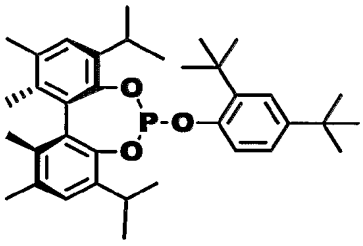

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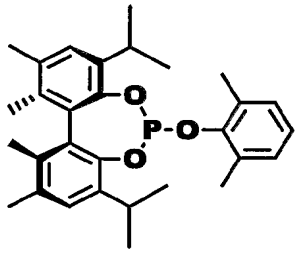

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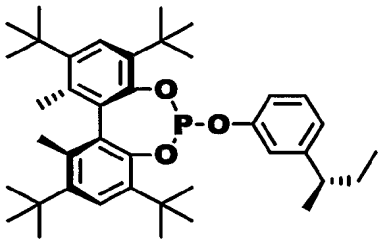

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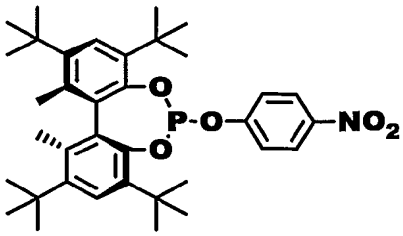

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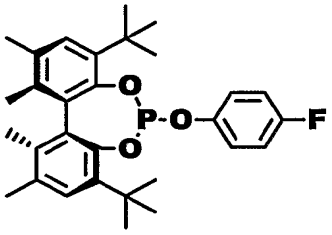

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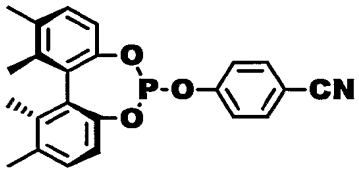

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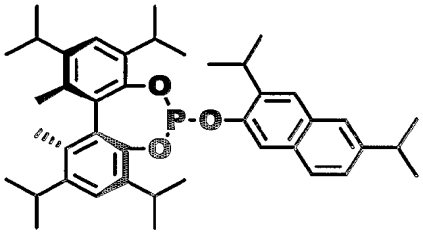

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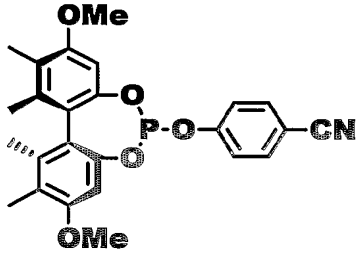

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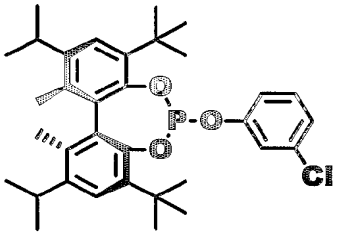

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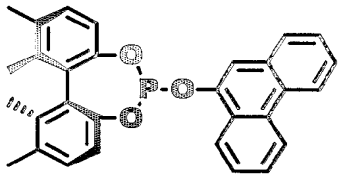

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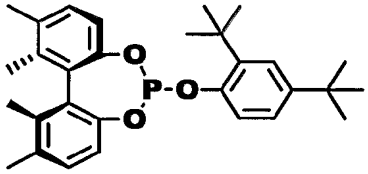

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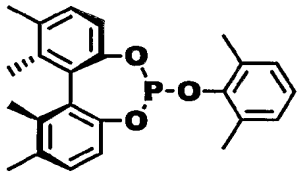

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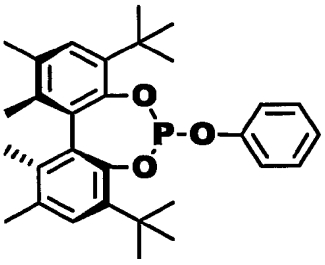

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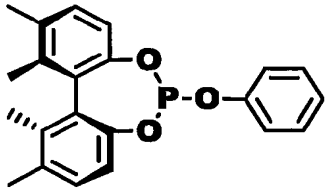

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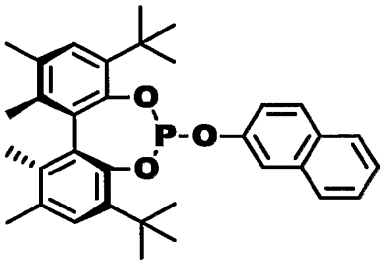

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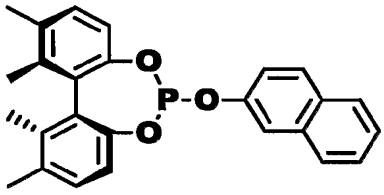

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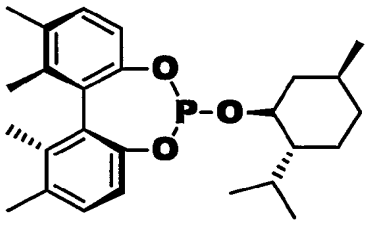

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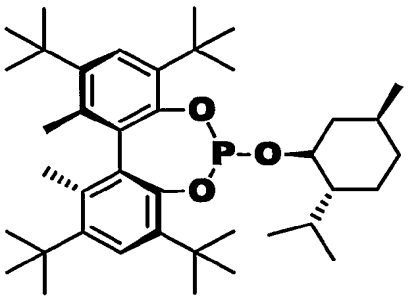

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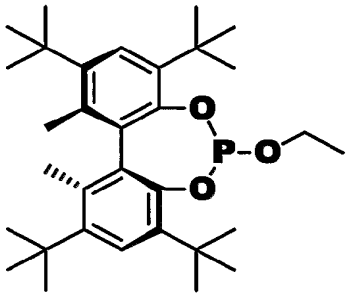

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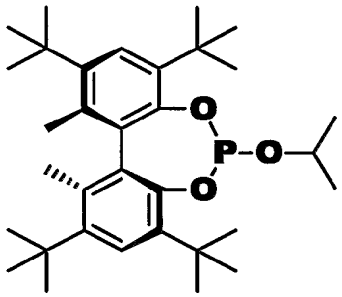

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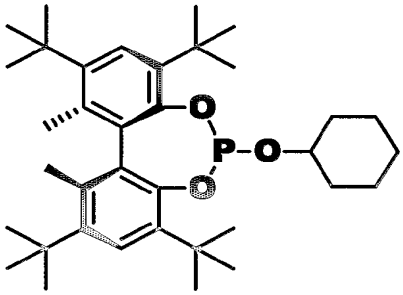

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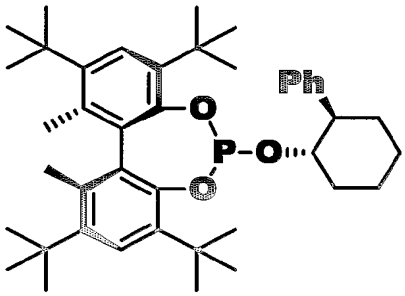

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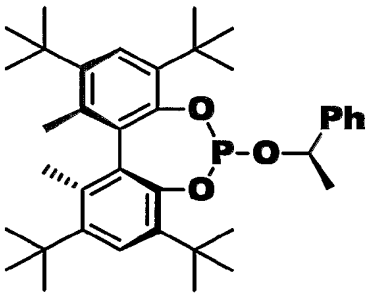

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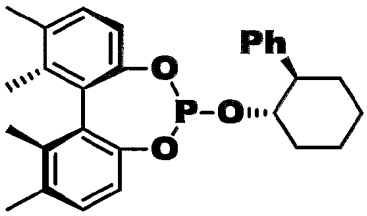

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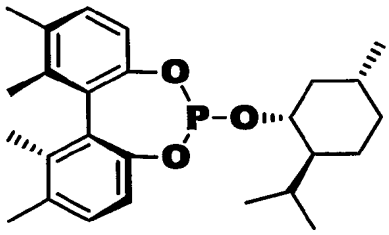

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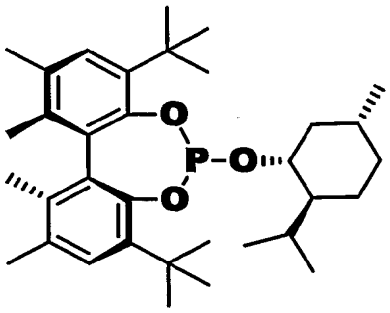

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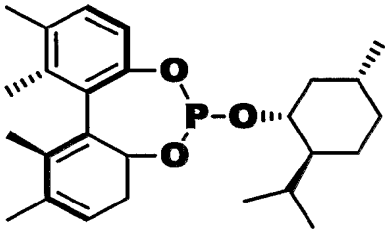

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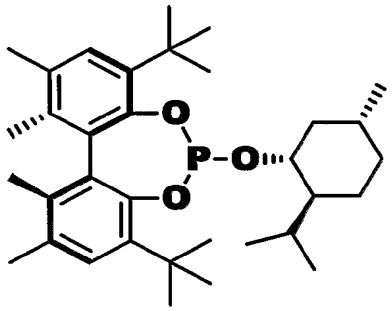

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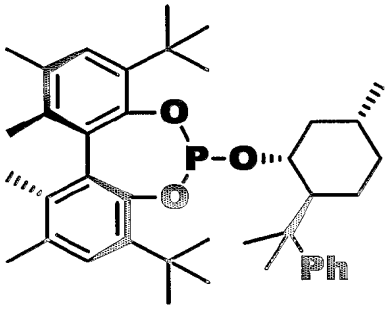

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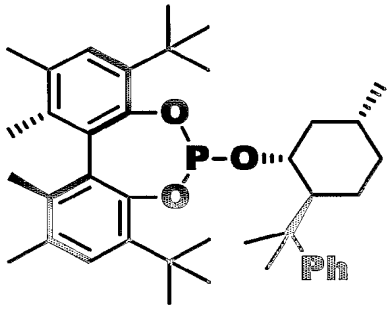

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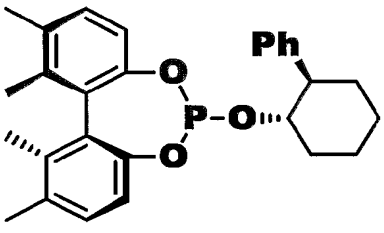

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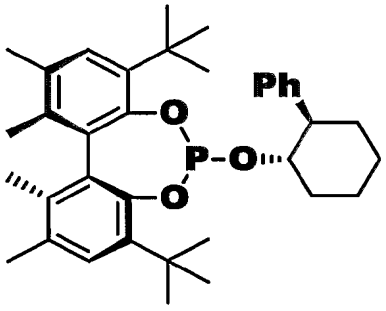

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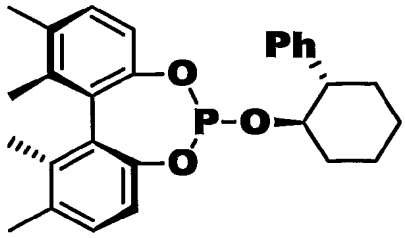

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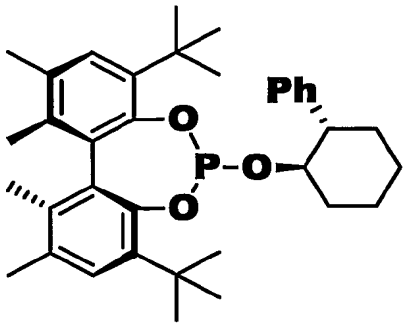

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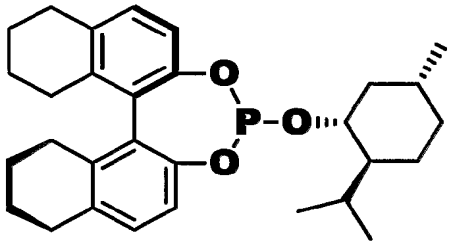

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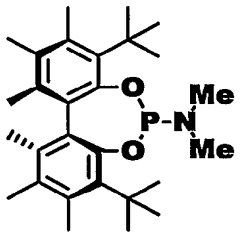

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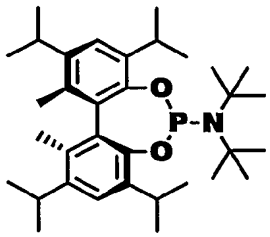

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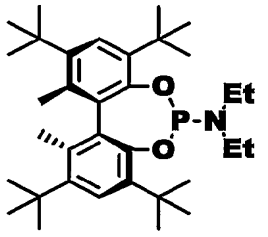

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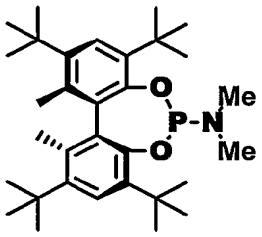

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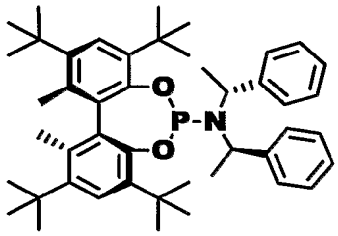

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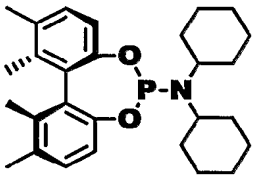

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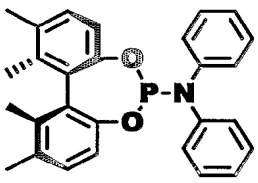

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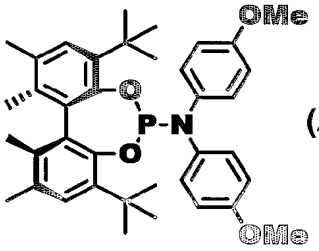

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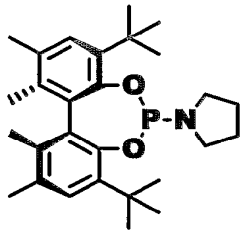

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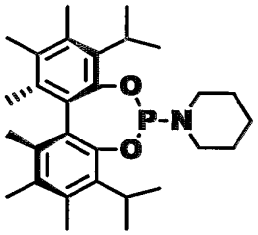

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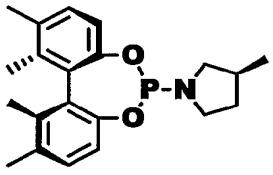

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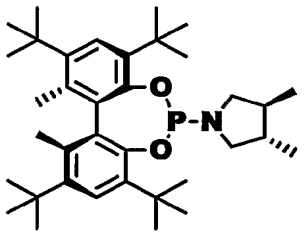

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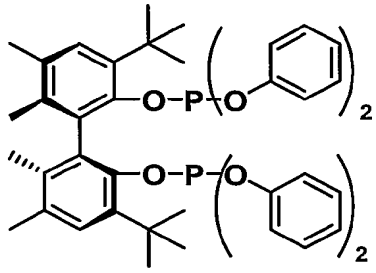

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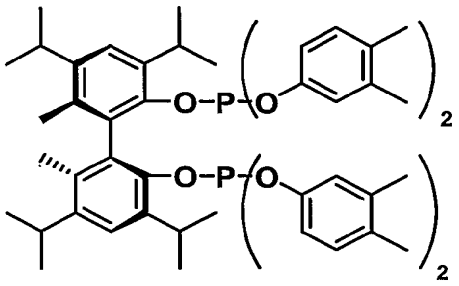

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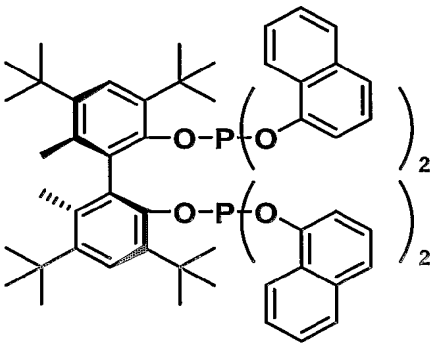

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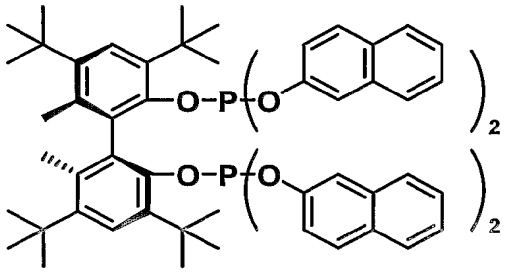

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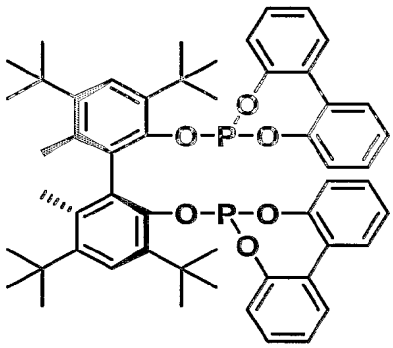

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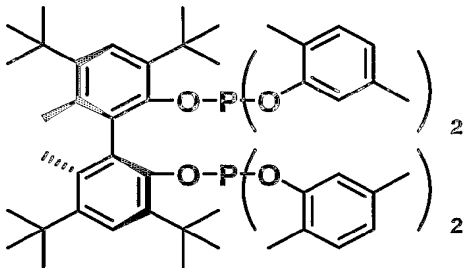

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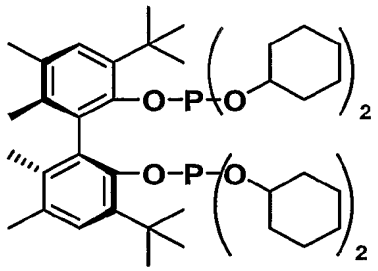

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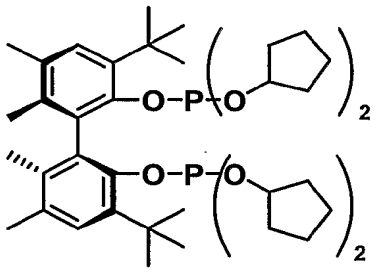

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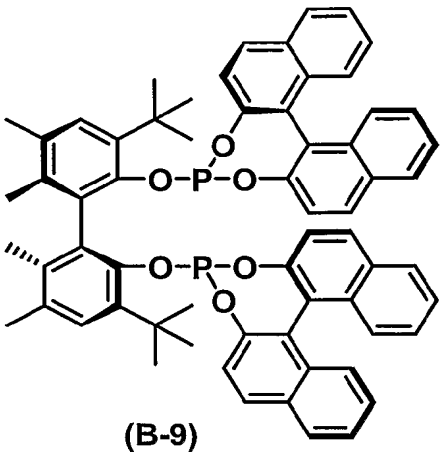

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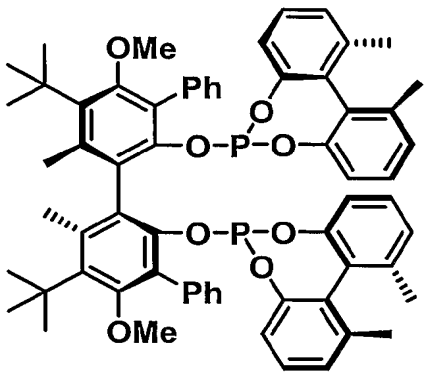

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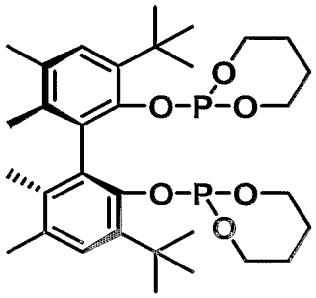

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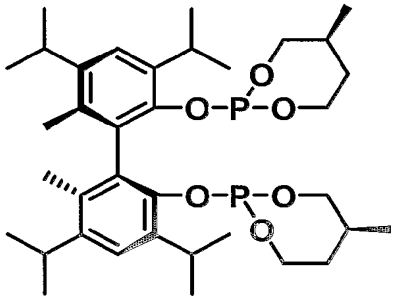

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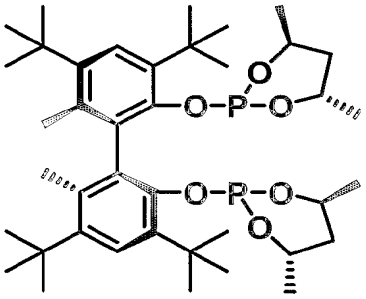

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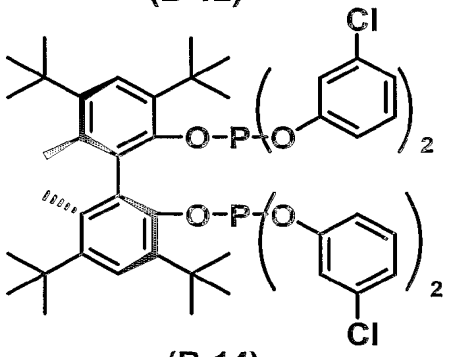

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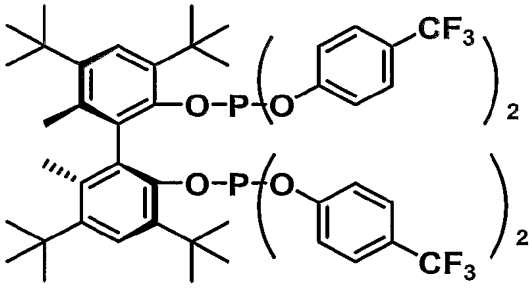

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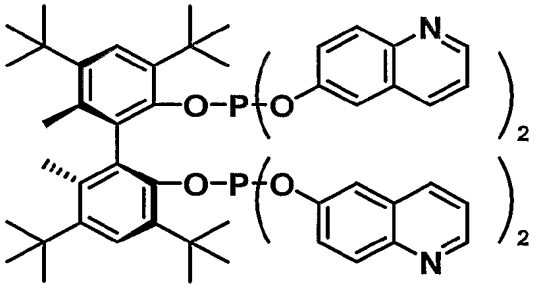

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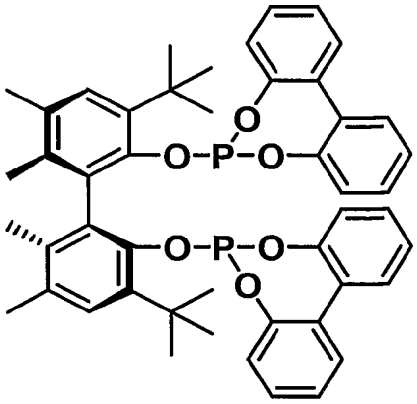

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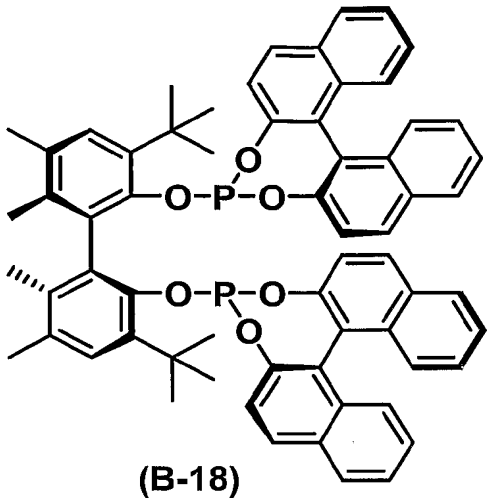

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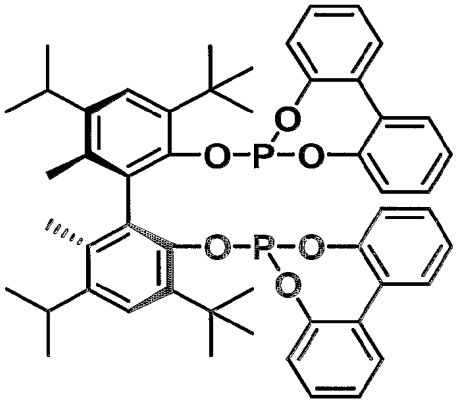

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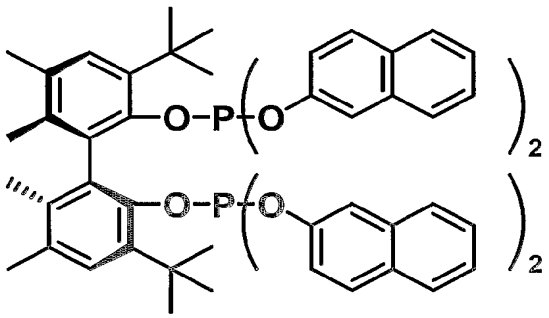

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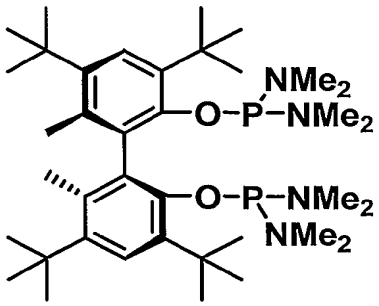

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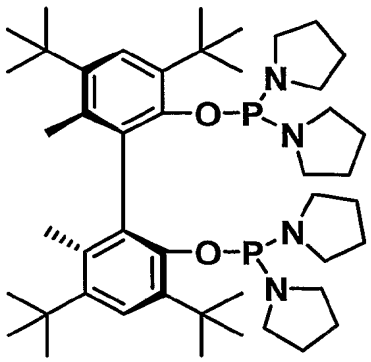

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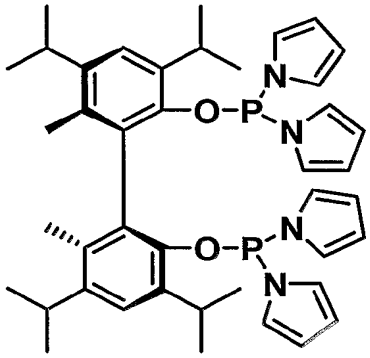

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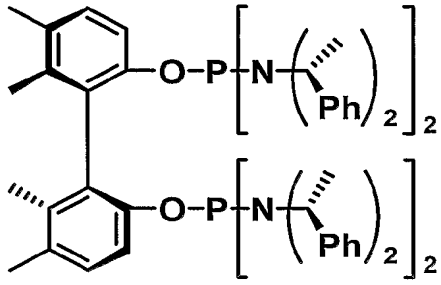

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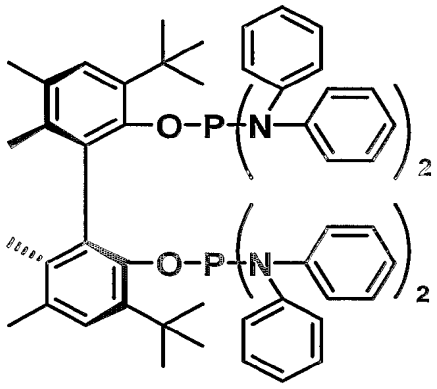

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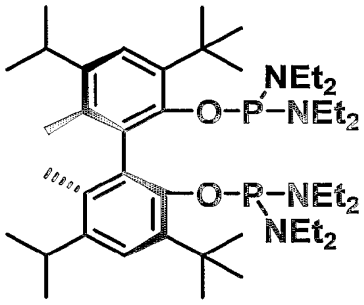
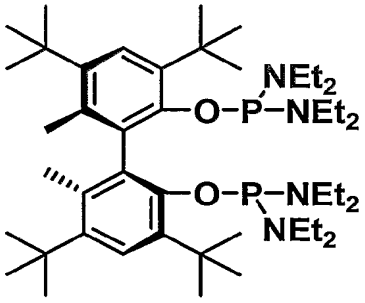


(B-26)



(B-27)

B. Catalyst comprising a transition metal or its compound and an optically active ligand of the present invention

B-1. Preparation of catalyst:

The catalyst can be prepared by reacting a transition metal or its compound with the optically active phosphite and/or phosphoramidite mentioned above.

The transition metals are those belonging to the groups 4 to 12 of the periodic table, and preferably those belonging to the groups 8 to 12 of the periodic table. Especially, Ru, Co, Rh, Ir, Ni, Pd, Cu, and Zn metals and their complexes are preferable. Examples of the transition metal compounds include metal halides such as metal chloride and metal bromide; metal hydrides; complexes having, as a ligand, an unsaturated hydrocarbon such as an olefin, a diene, and an acetylene; π-allyl complexes having an allyl group as a ligand; compounds having, as a ligand, a carboxylate group such as an acetoxy group and a benzoyloxy group; diketonate compounds having, as a ligand, a 1,3-diketone such as acetylacetone; and carbonyl compounds having carbon monoxide as a ligand. The transition metal compound may be made with such a ligand singly or a complex comprising a combination of multiple ligands. The form of the transition metal complex may be any form of a neutral complex or a cationic complex. In the case of the cationic complex, examples of its counter-anionic moiety include BF_4^-, PF_6^-, ClO_4^-, SbF_6^-, and CF_3COO^-.

Specific examples of the compounds of Ru, Co, Rh, Ir, Ni, Pd, Cu, or Zn include:

Ru compounds such as Ru(cot)(cod) (cot: cyclooctene, cod: cyclooctadiene), $Ru_3(CO)_{12}$, $RuCl_3$, $RuH_2(PPh_3)_4$, $RuH_2(CO)(PPh_3)_3$, $RuCl_2(PPh_3)_3$, $RuHCl(CO)(PPh_3)_3$, $[RuCl_2(cod)]_n$, and $RuCl_2(p\text{-}MeC_6H_4CHMe_2)$;

Co compounds such as $CoCl_2$, $CoCl_3$, and $Co_2(CO)_8$;

Rh compounds such as $RhCl_3$, $Rh(OAc)_3$, $Rh(CO)(acac)_2$ (acac: acetylacetonate), $Rh_4(CO)_{12}$, $Rh_6(CO)_{16}$, $RhCl(PPh_3)_3$, $RhCl(CO)(PMe_3)_2$, $[Rh(cod)Cl]_2$, $[Rh(cod)_2]BF_4$, $[Rh(cod)_2]PF_6$, $[Rh(cod)_2]SbF_6$, $[Rh(cod)_2]ClO_4$, $[Rh(cod)_2]OCOCF_3$, $RhH(PPh)_4$, and $Rh_2Cl_2(C_2H_4)_2$;

Ir compounds such as $IrCl_3$, $IrCl(CO)(PPh_3)_2$, $[Ir(cod)(PCy_3)(py)]PF_6$ (Cy: cyclohexyl, py: pyridine), and $[IrCl(cod)]_2$;

Ni compounds such as $NiCl_2$, $Ni(CO)_4$, $Ni(cod)_2$, $Ni(acac)_2$, $NiCl_2(PPh_3)_2$, $NiBr_2(PEt_3)_2$, $Ni(OAc)_2$ (Ac: acetyl), $Ni(PPh)_4$, $[(\eta\text{-}C_3H_5)NiCl]_2$, and $(\eta\text{-}C_3H_5)_2Ni$;

Pd compounds such as $PdCl_2$, $Pd(OAc)_2$, $Pd(acac)_2$, $(cod)PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $PdCl_2(CH_3CN)_2$, $Pd(dba)_2$ (dba: dibenzylideneacetone), $Pd_2(dba)_3$, $[(\eta\text{-}C_3H_5)PdCl]_2$, $[(\eta\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$, and $[(\eta\text{-}C_3H_5)Pd(cod)]PF_6$;

Pt compounds such as $PtCl_2$, H_2PtCl_6, $PtCl_2(cod)$, K_2PtCl_4, and $[PtCl_2(C_2H_4)]_2$;

Cu compounds such as CuCl, CuI, CuI_2, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, and $Cu(OCOCF_3)_2$; and

Zn compounds such as Et_2Zn and $ZnCl_2$.

The catalyst is formed by reacting a transition metal or its compound with an optically active phosphite and/or phosphoramidite. Since the optimum molar ratio varies depending upon the kind of the metal employed, it cannot be unequivocally defined. However, with any metal, it is necessary to carry out the reaction in a manner such that at least one equivalent of the phosphorus atom in a ligand is used per mole of the metal. This is because it may be considered that when the optically active phosphite and/or phosphoramidite is coordinated to the metal, an asymmetric environment is formed on the complex catalyst, and then the optically active product is formed through chirality transfer of this asymmetric environment. Taking into consideration this matter, in the case of the optically active bidentate phosphite and/or phosphoramidite, it is preferred that at least one molecule of the bidentate phosphite and/or phosphoramidite is coordinated to the metal atom in that two moles of the phosphorus atom are coordinated per mole of the metal.

In the formation of the catalyst, as described above, the molar equivalents of the phosphite and/or phosphoramidite that can be coordinated to the metal is limited and the optimum molar ratio of the phosphite and/or phosphoramidite varies depending upon the kind of the metal. Accordingly, it is not necessary to add an unnecessarily large quantity of the ligand. However, in the case of a complex, phenomena called dissociation equilibrium of the ligand is observed, which means that a ligand not coordinated to the complex may be present in the solution. Generally speaking, the molar equivalent of phosphorus atom in the ligand per mole of the metal is in the range of 1 to 20, and more preferably from 1 to 16. Whether or not the optically active phosphite and/or phosphoramidite is coordinated with the metal to form the optically active catalyst can be confirmed by the ^{31}P-NMR measurement of the reaction mixture. In general, a chemical shift of a peak assigned to the uncoordinated phosphorus atom is distinctly different from that of a peak assigned to the coordinated phosphorus atom. That is, the chemical shift of the phosphorus atom coordinated to the metal

is observed in a lower magnetic field as compared with that of the uncoordinated phosphorus atom.

The optically active catalyst can be prepared by mixing the metal or metal compound described above with the optically active phosphite and/or phosphoramidite.

It is not particularly required to isolate the optically active catalyst, thus prepared, and the reaction mixture can be used for the catalytic asymmetric reaction as it is. Accordingly, it is preferred that a solvent that is used for the formation of an optically active catalyst solution by mixing a metal compound with an optically active phosphite and/or phosphoramidite is the same as the solvent to be used for the catalytic asymmetric reaction. Examples of the solvent that can be suitably used include hydrocarbons such as hexane, heptane, toluene, xylene, and ethylbenzene; polar solvents such as THF, dibutyl ether, dioxane, DMF, DMSO, and DMI (dimethylimidazolidinone); and halogenated solvents such as dichloromethane, chloroform, dichloroethane, chlorobenzene, and dichlorobenzene.

The reaction temperature can be properly selected from the range of –100 °C to the boiling point of the solvent, and preferably from –78 °C to the boiling point of the solvent.

The reaction time is not particularly limited. Generally, the reaction time is selected from the range of 1 minute to 24 hours, and preferably from 2 minutes to 12 hours.

In the preparation of the optically active catalyst, the reaction atmosphere is not particularly limited for an inert gas atmosphere. However, it is preferable to carry out the reaction in an atmosphere of an inert gas such as nitrogen and argon.

The catalyst solution can be used for the subsequent catalytic reaction without isolating the catalyst. In the case where the isolation is performed, its method is not particularly limited, but the standard literature methods for the isolation of metal complexes can be used. For example, by adding a solvent in which the optically active catalyst complex is insoluble, the catalyst complex can be isolated as a solid. In addition, the catalyst complex can be purified by recrystallization.

B-2. Explanation of catalyst:

The optically active catalyst can be prepared by a combination of a transition metal or its compound with an optically active ligand as shown above. Since an embodiment in which the optically active ligand is coordinated to the transition metal compound varies depending upon the kind of the metal and the oxidation state of the metal, the asymmetric induction or chirality transfer from the catalyst to optically active products cannot be unequivocally

explained. However, a critically important issue here is the tight interaction between the optically active catalyst and the substrate, which creates asymmetric environment for efficient chirality transfer from the catalyst to the substrate. For achieving this, if the already coordinated optically active ligand is dissociated from the transition metal, the asymmetric environment is broken, hence such a situation is not desirable. Similarly, if a steric hindrance of the ligand itself is too large, it would become difficult for the ligand to coordinate to the transition metal, hence such a situation is not desirable. In order for the ligand to firmly coordinate to the metal, it may be considered that the bidentate ligand is better due to its chelation effect. However, even in the monodentate ligand, a firmly coordinated complex can be formed depending upon the structure of the ligand. Accordingly, it is not always correct to think that the optically active bidentate ligand gives a product with higher optical purity as compared with the optically active monodentate ligand.

In light of the above, what is important is the fact that the ligand is coordinated to the transition metal to form a rigid asymmetric environment irrespective of the monodentate or bidentate ligand.

From this point of view, in the present invention, the kinds of R^1 and/or R^5 and R^3 and/or R^7 are important.

When R^1 and/or R^5 is a hydrogen, a high optical yield can be achieved in the catalytic asymmetric reaction.

Furthermore, when R^1 and/or R^5 has a substituent that can change the steric hindrance and simultaneously delicately change an electronic effect, it is possible to provide an optically active chiral ligand that can achieve a high optical yield in various catalytic asymmetric reactions. When R^1 and/or R^5 has an optionally substituted secondary or tertiary hydrocarbon group having 3 to 20 carbon atoms, the reaction field is sterically and electronically influenced, whereby a catalytic stability and a high optical yield of the asymmetric catalytic reaction can be achieved.

When R^3 and/or R^7 has a substituent, specifically an optionally substituted hydrocarbon group having 1 to 20 carbon atoms or an optionally substituted alkoxy group having 1 to 10 carbon atoms, the thermal stability of the biphenol increases. In such a system, the approach of the substrate to an intermediate complex occurs from the side near the reaction field and thus a higher selectivity of the desired reaction in the catalysis can be realized, resulting in the achievement of a high optical yield in the catalytic asymmetric reaction.

The most preferable optically active ligands are the ones in which R^4 and R^8 each represents a methyl group. It has already been mentioned that in order to prevent the deterioration of the optical purity of the ligand, it is preferred that a rotational barrier of two phenyl groups is high with respect to the carbon-carbon bond connecting the two phenyl groups as an axis. However, in the case wherein R^4 and R^8 each represents an alkoxy group or a halogen, there is a possibility that the resulting ligand causes decomposition by hydrolysis of the substituent or elimination by reduction reaction, hence there is no guarantee that such optically active ligands can be used for reactions under a variety of reaction conditions. In contrast, in the case wherein an alkyl group such as methyl group is selected as the substituent, the substituent is poor in reactivity and is free from the foregoing possibility. Consequently, it is most preferable that both R^4 and R^8 represent a methyl group.

C. Process for the production of optically active compound by catalytic asymmetric reaction

C-1. General explanation:

The catalytic asymmetric reactions include many reactions such as hydrogenation reaction, oxidation reaction (such as epoxidation reaction and dihydroxylation reaction), hydroformylation reaction, hydrosilylation reaction, allylic substitution reaction, aldol reaction, and Michael addition reaction. Among these reactions, preferable catalytic asymmetric reactions for the present invention are the ones in which an optically active complex catalyst having an optically active phosphorus compound as ligand contributes effectively. This is because the asymmetric reaction proceeds through chirality transfer in which the optically active phosphorus ligand is the chiral source.

More specifically, the preferable reactions are hydrogenation reaction using a catalyst made of Ru, Rh, Ir, Pd, or Pt; hydroformylation reaction using a catalyst made of Co, Rh, or Pt; hydrosilylation reaction using a catalyst made of Pd, Rh, Ir, or Pt; Michael addition reaction using a catalyst made of Cu or Zn; and allylic substitution reaction using a Pd or Ir complex. Of these, hydrogenation reaction using a catalyst made of Ru or Rh; hydroformylation reaction using a catalyst made of Rh; hydrosilylation reaction using a catalyst made of Rh, Ir, or Pd; Michael addition reaction using a catalyst made of Cu or Zn; and allylic substitution reaction using a catalyst made of Pd or Ir are particularly preferable because industrially useful compounds can be synthesized.

As the substrates for performing these reactions, prochiral compounds must be selected. The prochiral compound as referred to herein means a compound that can induce at

least one chiral center (optically active center at carbon) to the product formed after the reaction. Examples of the prochiral compounds include those having carbon-carbon double bonds and dissymmetric ketones. As so far as dissymmetric ketones are concerned, for example, methyl ethyl ketone and acetophenone are typical prochiral compounds, which give the corresponding alcohols bearing a chiral center at the 2-position by hydrogenation reaction.

C-2. Asymmetric hydroformylation reaction:

The hydroformylation reaction is a reaction in which an olefinic compound is reacted with a mixed gas of carbon monoxide and hydrogen (generally called an oxo gas) in the presence of a catalyst to produce the corresponding aldehyde. Aldehydes are important intermediates in chemical, pharmaceutical, and agricultural industries because aldehydes can be converted to alcohols upon reduction, to carboxylic acids upon oxidation, to various condensation products via aldol reaction, imine formation, hydrazide formation and other known reactions.

In the hydroformylation reaction, a formyl group and a hydrogen are introduced into two carbons of the olefinic compound, respectively. Whether a chiral carbon is formed or not depends upon the position of a formyl group and a hydrogen to be introduced. Accordingly, in the present invention, it is important to control the reaction process in a regioselective manner such that the chiral carbon is generated by hydroformylation reaction.

The asymmetric hydroformylation reaction can be carried out using a catalyst comprising an Rh, Co or Pt metal or its compound and an optically active phosphite and/or phosphoramidite of the present invention in the presence or absence of a solvent.

With respect to the Rh, Co or Pt compounds and the optically active phosphites and/or phosphoramidites, the same as described above can be referred to. The amount of the catalyst to be used is usually 0.1 ppm by mole concentration or more, preferably 1 ppm or more, and more preferably 5 ppm or more, and usually 1/5 moles with regard to the substrate concentration or less, preferably 1/10 moles or less, more preferably 1/50 moles or less, and most preferably 1/100 moles or less.

A solvent is not always necessary for the reaction, and a substrate itself may be used as the solvent. Examples of the solvents include hydrocarbons such as hexane, heptane, decane, cyclohexane, toluene, and xylene; ethers such as THF, diethyl ether, and dioxane; esters such as ethyl acetate, butyl acetate, and methyl benzoate; aprotic polar solvents such as DMF, DMSO, and DMI; and alcohols such as methanol, ethanol, and butanol. Among these, solvents that can uniformly dissolve the optically active catalyst and the substrate are

preferable. Thus, hydrocarbons such as toluene and ethers such as THF are preferable solvents.

The hydrogen and carbon monoxide mixing ratio of the oxo gas (H_2/CO) is not particularly limited, but is usually from 10/1 to 1/10, and preferably from 2/1 to 1/2. The reaction pressure is selected from the range of 0.01 MPa to 30 MPa, and preferably from 0.05 MPa to 20 MPa.

The reaction temperature is preferably selected from the range of –30 °C to 200 °C, and more preferably from –20 °C to 150 °C. A temperature range of 0 °C to 100 °C is particularly preferred because the operation is easy and economical besides a high optical purity can be achieved.

As the substrate of the reaction, a prochiral olefinic compound is used. Examples of the prochiral olefinic compounds include styrenes (such as styrene, p-cyanostyrene, p-fluorostyrene, 1-vinyl-4-isobutylbenzene, pentafluorostyrene, and 1-propenylbenzene), alkenylnaphthalenes (such as 2-vinylnaphthalene, 1-vinyl-4-fluoronaphthalene, and 2-vinyl-6-methoxynaphthalene), N-alkenylphthalimides (such as N-vinylphthalimide, N-2-propenylphthalimide, and N-styrylphthalimide), vinyl acetate, N-alkenyl amides (such as N-vinylacetamide, N-vinyltrifluoroacetamide, and N-vinylbenzoic acid amide), 2-butene, indene, dihydronaphthalene, 3-hexene, methyl acrylate, various dehydroamino acids, 2,5-dihydrofuran, N-t-butoxycarbonyl-2,5-dihydropyrrole, N-acetyl-2,5-dihydropyrrole, N-t-butoxycarbonyl-2,3-dihydropyrrole, 2-propenylbenzene, and methyl methacrylate.

C-3. Asymmetric hydrogenation reaction:

The asymmetric hydrogenation reaction as referred to herein means hydrogenation reaction of a substrate bearing a prochiral carbon-carbon double bond, carbon-oxygen double bond or carbon-nitrogen double bond, and the substrate is not particularly limited. In other words, any of prochiral olefinic compounds, carbonyl compounds, and imine compounds can be used as the substrate.

The hydrogenation reaction is carried out with hydrogen using an optically active catalyst comprising a Ru, Rh, Ir, Pd or Pt metal or its compound and an optically active ligand of the present invention in the presence or absence of a solvent.

The amount of the catalyst to be used is usually 0.1 ppm by mole concentration or more, preferably 1 ppm or more, and more preferably 5 ppm or more, and usually 1/5 moles with respect to the substrate concentration or less, preferably 1/10 moles or less, more

preferably 1/50 moles or less, and most preferably 1/100 moles or less. Examples of the solvents include hydrocarbons such as hexane, heptane, decane, cyclohexane, toluene, and xylene; ethers such as THF, diethyl ether, and dioxane; esters such as ethyl acetate, butyl acetate, and methyl benzoate; aprotic polar solvents such as DMF, DMSO, and DMI; and alcohols such as methanol, ethanol, and butanol. Among these, solvents that do not react with hydrogen under the reaction conditions are preferable, and hydrocarbons such as toluene and ethers such as THF are preferable.

Gaseous molecular hydrogen may be used as the hydrogen source. Alternatively, a compound capable of supplying hydrogen may be used. Examples of such compounds capable of supplying hydrogen include isopropyl alcohol and formic acid. A partial pressure of the hydrogen is selected from the range of 0.001 MPa to 30 MPa, and an inert gas to the reaction may be co-present. The partial pressure of the hydrogen is preferably in the range of 0.01 MPa to 20 MPa, and more preferably 0.05 MPa to 15 MPa.

The reaction temperature is preferably selected from the range of –30 °C to 200 °C, and more preferably from –20 °C to 150 °C. A temperature range of 0 °C to 100 °C is particularly preferred because the operation is easy and economical besides a high optical purity can be achieved.

C-4. Other asymmetric catalytic reactions:

When an Si-H bond-containing compound such as trichlorohydrosilane, triethoxyhydrosilane, diphenylsilane, and triphenylsilane is used in place of hydrogen in the hydrogenation reaction as shown in C-3, the reaction becomes hydrosilylation reaction. The substrates for this reaction include the compounds bearing a prochiral carbon-carbon double bond, carbon-oxygen double bond or carbon-nitrogen double bond, but the present invention is not particularly limited thereto. The reaction is carried out in the presence or absence of a solvent, and optionally under an atmosphere of an inert gas such as nitrogen.

The amount of the catalyst to be used is usually 0.1 ppm by mole concentration or more, preferably 1 ppm or more, and more preferably 5 ppm or more, and usually 1/5 moles with respect to the substrate concentration or less, preferably 1/10 moles or less, more preferably 1/50 moles or less, and most preferably 1/100 moles or less.

Examples of the solvents include hydrocarbons such as hexane, heptane, decane, cyclohexane, toluene, and xylene; ethers such as THF, diethyl ether, and dioxane; esters such as ethyl acetate, butyl acetate, and methyl benzoate; aprotic polar solvents such as DMF,

DMSO, and DMI; and alcohols such as methanol, ethanol, and butanol. Among those, solvents that do not react with hydrosilanes are preferable. Thus, hydrocarbons such as toluene and ethers such as THF are preferable.

The reaction temperature is properly selected from the range of –78 °C to 200 °C, and more preferably from 0 °C to 100 °C.

The allylic substitution reaction can be carried out by reacting an allyllic compound (such as 2-butenyl acetate) as the substrate with an anion of an ester using an optically active catalyst comprising a Pd or Ir compound and an optically active ligand of the present invention in the presence or absence of a solvent.

The amount of the catalyst to be used is usually 0.1 ppm by mole concentration or more, preferably 1 ppm or more, and more preferably 5 ppm or more, and usually 1/5 moles with respect to the substrate concentration or less, preferably 1/10 moles or less, more preferably 1/50 moles or less, and most preferably 1/100 moles or less.

As the substrate for this process, a compound which can form a π-allyl complex with a Pd or Ir compound is preferred on the basis of the reaction mechanism. Examples of the leaving group (a substituent at the allyllic position of a substrate) include halogens such as chlorine and bromine, an acetoxy group, a benzoyloxy group, and a trifluoroacetoxy group.

Examples of the solvent include hydrocarbons such as hexane, heptane, decane, cyclohexane, toluene, and xylene; ethers such as THF, diethyl ether, and dioxane; esters such as ethyl acetate, butyl acetate, and methyl benzoate; aprotic polar solvents such as DMF, DMSO, and DMI; and alcohols such as methanol, ethanol, and butanol. Among these, solvents that are intert under the reaction conditions are preferable. Thus, hydrocarbons such as toluene and ethers such as THF are preferable.

The reaction temperature is properly selected from the range of –78 °C to 200 °C, and more preferably from -20 °C to 100 °C.

In general, the asymmetric addition reaction of a nucleophile to an α,β-unsaturated carbonyl compound is called asymmetric Michael addition reaction. Examples of the substrates include α,β-unsaturated ketones such as cyclopentenone, cyclohexenone, and chalcone; and α,β-unsaturated esters such as methyl 2-butenoate. Examples of nucleophiles that can be suitably used include dialkylzinc compounds, with diethylzinc being particularly preferred. As the optically active catalysts, Ni and Cu compounds are preferred, and Cu compounds are particularly preferred.

The amount of the catalyst to be used is usually 0.1 ppm by mole concentration or more, preferably 1 ppm or more, and more preferably 5 ppm or more, and usually 1/5 moles with respect to the substrate concentration or less, preferably 1/10 moles or less, more preferably 1/50 moles or less, and most preferably 1/100 moles or less.

The reaction temperature can be properly selected from the range of −100 °C to 100 °C, preferably from -20 °C to 50 °C, and more preferably from 0 °C to 25 °C.

The following non-limiting examples are illustrative of the present invention. It should be noted that various changes would be made in the above examples and processes therein without departing from the scope of the present invention. For this reason, it is intended that the illustrative embodiments of the present application should be interpreted as being illustrative and not limiting in any sense.

EXAMPLES

EXAMPLES 1-13

Synthesis of monophosphite ligands

Synthesis of [(S)-3,3'-di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl]-((1S,2R)-(+)-2-phenyl-1-cyclohexyl)phosphite (A-40) is described as a typical example.

To a solution of (1S,2R)-(+)-2-phenylcyclohexan-1-ol (154 mg, 0.88 mmol) in 5 mL of CH_2Cl_2 under nitrogen was added PCl_3 (0.15 mL, 1.76 mmol), and the mixture was allowed to stir at room temperature for 1 h. The solvent and excess PCl_3 were evaporated under reduced pressure, and the resulting oil was redissolved in 2 mL of THF. To this solution was added a mixture of 2,2'-dihydroxyl-3,3'-di-tert-butyl-5,5',6,6'-tetramethylbiphenyl (312 mg, 0.88 mol) and Et3N (0.37 mL, 2.64 mmol) in 3 mL of THF. Upon addition, the formation of white precipitate was observed immediately. The mixture was stirred at room temperature overnight. The resulting precipitate was filtered off and the solution was concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (eluant: hexane/dichloromethane = 10/1).) to afford [(S)-3,3'-di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl]-((1S,2R)-(+)-2-phenyl-1-cyclohexyl)phosphite (A-40) as white solid (368 mg, 75% yield): mp 62.0-64.0 oC; $[\alpha]_D^{22} = +320.5$ (CH_2Cl_2, c 0.68); ^{1}H NMR (400 MHz, C_6D_6) δ 0.81-1.74 (m, 8H), 1.47 (s, 9H), 1.49 (s, 9H), 1.63 (s, 3H), 1.65 (s, 3H), 1.99 (s, 3H), 2.04 (s, 3H), 2.25-2.30 (m, 1H), 2.59-2.65 (m, 1H), 6.91-7.15 (m, 7H); ^{31}P NMR (162 MHz, C_6D_6) δ 139.9. HRMS(FAB) calcd. for $C_{36}H_{47}O_3P$ $[M+H]^+$ 559.3341, found 559.3341 (Δ = 0.0 ppm).

In the same manner, other optically active monophosphite ligands were synthesized. Yields and characterization data for those monophosphite ligands are shown below.

[(S)-3,3'-Di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl](phenyl)phosphite (A-21): 85% yield; mp 158.5-160.0 °C; $[\alpha]_D^{22}$ + 318.9 (c 0.63, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 1.45 (s, 9H), 1.55 (s, 9H), 1.68 (s, 6H), 2.00 (s, 6H), 6.71-7.10 (m, 5H), 7.15 (s, 1H), 7.22 (s, 1H); ^{31}P NMR (162 MHz, C_6D_6) δ 133.9. HRMS (FAB) calcd. for $C_{30}H_{37}O_3P$ 476.2480, found 476.2479 (Δ = 0.3 ppm).

[(S)-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl](phenyl)phosphite (A-22): colorless viscous oil; 25% yield; ^1H NMR (400 MHz, C_6D_6) δ 1.74 (s, 3H), 1.76 (s, 3H), 1.92 (s, 6H), 6.76-7.02 (m, 9H); ^{31}P NMR (162 MHz, C_6D_6) δ 38.9.

[(S)-3,3'-Di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl](2-naphthyl)phosphite (A-23): 70% yield; mp 72.5-75.5 °C; $[\alpha]_D^{22}$ + 283.3 (c 0.72, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 1.46 (s, 9H), 1.58 (s, 9H), 1.70 (s, 3H), 1.71 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 7.04-7.13 (m, 2H), 7.16 (s, 1H), 7.20 (dd, 1H, J = 9.2 Hz, 2.0 Hz)7.25 (s, 1H), 7.33 (d, 1H, J = 9.2 Hz), 7.40 (s, 1H), 7.42 (s, 1H), 7.51 (s, 1H); ^{31}P NMR (162 MHz, C_6D_6) δ 132.9. HRMS (FAB) calcd. for $C_{30}H_{37}O_3P$ $[M+H]^+$ 527.2715, found 527.2714 (Δ = 0.2 ppm).

[(S)-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl] (2-naphthyl)phosphite (A-24): ^1H NMR (400 MHz, C_6D_6): colorless viscous oil; 66% yield; δ 1.77 (s, 6H), 1.92 (s, 3H), 1.93 (s, 3H), 6.86 (d, 2H, J = 8.0) 7.0-7.7 (m, 7H), 7.37 (d, 2H, J = 8.8 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 136.5. HRMS (FAB) calcd for $C_{26}H_{23}O_3P$ $[M+H]^+$ 415.1463, found 415.1464 (Δ = 0.1 ppm).

[(S)-3,3'-di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl]((-)-menthyl)phosphite (A-34): 63% yield; mp 57.0-59.0 °C; $[\alpha]_D^{22}$ + 230.5 (c 0.73, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 0.50-1.84 (m, 8H), 0.61 (d, 3H, J = 6.4 Hz), 0.80 (d, 3H, J = 6.8 Hz), 0.86 (d, 3H, J = 7.2 Hz), 1.57 (s, 9H), 1.60(s, 9H), 1.67 (s, 3H), 1.70 (s, 3H), 2.01(s, 3H), 2.02 (s, 3H), 2.43-2.45 (m, 1H), 4.09-4.12 (m, 1H), 7.17 (s, 1H), 7.22 (s, H); ^{31}P NMR (162 MHz, C_6D_6) δ 137.9. HRMS (FAB) calcd. for $C_{34}H_{51}O_3P$ $[M-H]^+$ 537.3498, found 537.3499 (Δ = - 0.3 ppm).

[(S)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl]((-)-menthyl)phosphite (A-33): colorless viscous oil; 76% yield; ^{1}H NMR (400 MHz, C_6D_6): δ 0.3-1.5 (m, 8H), 0.67 (d, 3H, J = 6.0 Hz), 0.84 (d, 3H, J = 6.8 Hz), 0.89 (d, 3H, 7.0 Hz), 1.75 (s, 3H), 1.76 (s, 3H), 1.94 (s, 6H), 2.4 2.6 (m, 1H), 3.9-4.1 (m, 1H), 6.87 (d, 1H, J = 8.0), 6.96 (d, 1H, J = 8.0).7.12 (apparent t, 2H, J = 8.4 Hz); ^{31}P NMR (162 MHz, C_6D_6): δ 147.1.

[(R)-3,3'-Di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl]((-)-menthyl)phosphite (A-36): 68% yield; mp 128.0-130.5 °C; $[\alpha]_D^{22}$ – 336.9 (c 0.87, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) δ 0.56-1.94 (m, 8H), 0.63 (d, 3H, J = 5.2 Hz), 0.64 (d, 3H, J = 4.8 Hz), 0.73 (d, 3H, 6.4 Hz), 1.57 (s, 9H), 1.59 (s, 9H), 1.68 (s, 6H), 2.01 (s, 3H), 2.02 (s, 3H), 2.24-2.32 (m, 1H), 4.04-4.08 (m, 1H), 7.17 (S, 1H), 7.19(S, 1H); ^{31}P NMR (162 MHz, C_6D_6) δ 141.4. HRMS (FAB) calcd. for $C_{34}H_{51}O_3P$ $[M+H]^+$ 539.3654, found 539.3656 (Δ = -0.4 ppm).

[(R)-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl]((-)-menthyl)phosphite (A-35): colorless viscous oil; 75% yield; ^{1}H NMR (400 MHz, CD_2C_{l2}): δ 0.7-1.8 (m, 8H), 0.82 (d, 3H, J = 7.2 Hz), 0.89 (d, 3H, J = 7.2 Hz), 0.98 (d, 3H, 6.4 Hz), 2.02 (s, 6H), 2.31 (s, 6H), 2.1 2.2 (m, 1H), 4.0-4.2 (m, 1H), 6.84 (d, 1H, J = 8.0), 6.99 (d, 1H, J = 8.0).7.17 (apparent t, 2H, J = 7.6 Hz); ^{31}P NMR (162 MHz, C_6D_6): δ 148.8.

[(S)-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl](-((1S,2R)-(+)-2-phenyl-1-cyclohexyl)phosphite (A-39): 61% yield; mp 149.0-151.0 °C; $[\alpha]_D^{22}$ +200.6 (c 0.58, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) δ 0.81-1.63 (m, 7H), 1.69 (s, 3H), 1.72(s, 3H), 1.88 (s, 3H), 1.94 (s, 3H), 2.11-2.15 (m, 1H), 2.39-2.46 (m, 1H), 4.11-4.15 (m, 1H), 6.75 (dd, J = 21.6, 8.0 Hz, 2 H), 6.89 (dd, J = 24.4, 8.0 Hz, 2H), 7.11-7.24 (m, 5H); ^{31}P NMR (162 MHz, C_6D_6) δ 146.9. HRMS (FAB) calcd. for $C_{28}H_{31}O_3P$ $[M+H]^+$ 447.2089, found 447.2088 (Δ = 0.2 ppm).

[(S)-3,3'-Di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl]((1R,2S)-(+)-2-phenyl-1-cyclohexyl)phosphite (A-42): 60% yield; mp 67.0-69.0 °C; $[\alpha]_D^{22}$ +250.2 (c 0.88, CH2Cl2); ^{1}H NMR (300 MHz, CD2Cl2) δ 1.26 (s, 9H), 1.56 (s, 9H), 1.33-1.91 (m, 8H), 1.76 (s, 3H), 1.80 (s, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 2.61-2.67 (m, 1H), 4.36-4.39 (m, 1H), 7.14-

7.31 (m, 7H); ^{31}P NMR (101 MHz, CD_2Cl_2) δ 137.9. HRMS (FAB) calcd. for $C_{36}H_{47}O_3P$ [M-H]$^+$ 557.3185, found 557.3185 (Δ = - 0.1 ppm).

[(S)-3,3'-Di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl]((-)-8-phenylmenthyl)phosphite (A-37): 81% yield; mp 137.0-139.0 °C; $[\alpha]_D^{22}$ +296.7 (c 0.60, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 0.57 (d, J = 6.6 Hz, 3H), 0.74-1.36 (m, 8H), 1.43 (s, 3H), 1.53 (s, 3H), 1.60 (s, 9H), 1.64 (s, 9H), 1.71 (s, 3H), 1.83 (s, 3H), 2.07 (s, 3H), 2.14 (s, 3H), 4.30-4.39 (s, 1H), 7.01-7.33 (m, 7H); ^{31}P NMR (101 MHz, C_6D_6) δ 133.7.

[(R)-3,3'-Di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl]((-)-8-phenylmenthyl)phosphite (A-38): 63% yield; mp 75.0-77.0 °C; $[\alpha]_D^{22}$ -226.2 (c 0.43, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 0.67 (d, J = 6.3 Hz, 3H), 0.50-1.50 (m, 7H), 1.20 (s, 3H), 1.37 (s, 3H), 1.68 (s, 9H), 1.69 (m, 9H), 1.73 (s, 3H), 1.78(s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.53-2.64 (m 1H), 4.21-4.39 (m, 1H), 7.01-7.27 (m, 7H); ^{31}P NMR (101 MHz, C_6D_6) δ 145.3.

((R)-5,6,7,8,5',6',7',8'-Octahydro-1,1'-binaphthyl-2,2'-diyl)((-)-menthyl)phosphite (A-43): 50% yield; mp 153.0-155.0 °C; $[\alpha]_D^{22}$ –172.9 (c 0.57, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) δ 0.68 (d, J = 7.2 Hz, 3H), 0.76 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H), 1.03-1.49 (m, 9H), 2.13-2.62 (m, 8H), 3.99-4.08 (m, 1H), 6.80-7.15 (m, 4H); ^{31}P NMR (162 MHz, C_6D_6) δ 147.0.

EXAMPLE 14

Preparation of Monophosphite, A-4

A 500 mL three-necked, round-bottomed flask equipped with a dropping funnel, a magnetic stirring bar was flushed with nitrogen. To a dry THF solution (90 mL) of PCl_3 (10.80 g, 79 mmol) was added (S)-3,3',5,5'-tetra-t-butyl-6,6'-dimethyl-2,2'-biphenol (30.00 g, 68 mmol) and triethylamine (21 mL, 150 mmol) in 120 mL THF was during 40 min from additional funnel at 0 °C. Reaction mixture was stirred for 1hr, triethylamine hydrochloride formed was filtered off under nitrogen atmosphere. The filtrate including excess amount of PCl_3 and the solvent was removed under reduced pressure and residue was dried in vacuo. Cyclic monochlorophosphite was obtained as a white solid (30.53 g, yield 77.1%).

This material was used for next step without further purification.

^{31}P NMR (toluene, triphenylphosphate in C_6D_6 was used as internal standard)

δ 163.19 ppm

To a THF solution (35 mL) of cyclic monochlorophosphite (5.03 g, 10 mmol) was added phenol (0.94 g, 10 mmol) and triethylamine (1.5 mL, 11 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen and the mixture was stirred at 0 °C for 2 hrs.

^{31}P NMR (THF solution, triphenylphosphate in C_6D_6 was used for internal standard) δ 130.16 ppm

Solvent was removed under reduced pressure and residue was added 50 ml of toluene and 50 mL of water. Organic layer was separated and washed with 50 mL of $NaHCO_3$ aq., and 50 mL of brine. The organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, residual oily product was washed with acetonitril and methanol repeatedly. A-4 was obtained as white powders (1.10g, 19.6%)

A-4: ^1H NMR ($CDCl_3$) δ 1.43 (d, 18H, d=2.8 Hz), 1.46 (s, 18H), 1.46 (s, 18H), 2.00 (s, 3H), 2.03 (s, 13H), 6.99 (d, 2H, J=7.8 Hz), 7.06 (t, 1H, J=7.3 Hz), 7.42 (d, 2H, J=5.8 Hz)

^{31}P NMR ($CDCl_3$) δ 131.07 ppm

EXAMPLES 15-18

Synthesis of diphosphite ligands

Synthesis of 2,2'-bis[{(S)-1,1'-binaphthyl-2,2'-dioxy}phosphinyloxy]-(S)-3,3'-di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl (B-18) is described as typical example.

To a solution of 2,2'-dihydroxyl-3,3'-di-tert-butyl-5,5',6,6'-tetramethylbiphenyl (0.27 g, 1.54 mmol) in tetrahydrofuran (5 mL) was added slowly 2.5 M butyllithium (0.68 mL, 1.69 mmol) in hexanes at room temperature under nitrogen. The solution was heated to reflux and stirred for 2 h. The progress of the reaction was monitored by removing an aliquot (0.1 mL) from the reaction mixture and quenching with chlorotrimethylsilane, diluting with tetrahydrofuran, filtering and analyzing by GC/MS. To another reaction flask equipped with a reflux condenser, containing to (S)-2,2'-binapthol (0.44 g, 1.54 mmol) was added phosphorous trichloride (1 mL, 0.77 mmol), and the mixture was heated to reflux for 3 hrs. Then, excess phosphorous trichloride was removed in vacuo and the resulting oily residue azeotroped with toluene (1 mL x 4) to remove any residual phosphorous trichloride. The resulting oil was diluted with tetrahydrofuran (5 mL) and added by cannula to the solution of the dilithium salt of the dihydroxybiphenyl prepared above at 0 °C. The mixture was allowed

to warm to room temperature and stirred for 15 h. The reaction was quenched with water (5 mL), the aqueous layer separated, and extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$) filtered and concentrated in vacuo to give oily crude product. The crude product was purified by column chromatography on silica gel (hexane/dichloromethane = 5/1) to afford 2,2'-bis[{(S)-1,1'-binaphthyl-2,2'-dioxy}phosphinyloxy]-(S)-3,3'-di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl (B-18) (0.22 g, 29%) as white solid: mp 131-165 °C; $[\alpha]_D^{22}$ +203.1 (CH_2Cl_2, c 0.43); ^{1}H NMR (400 MHz, C_6D_6): δ 1.46 (s, 9H), 1.61 (s, 9H), 1.72(s, 3H), 1.84 (s, 3H), 2.01(s, 3H), 2.08 (s, 3H), 6.77-7.80 (m, 14H); ^{31}P NMR (162 MHz, C6D6) δ 144.1. HRMS (FAB) calcd. for $C_{64}H_{56}O_6P_2$ $[M+H]^+$ 983.3630, found 983.3634 (Δ = -0.4 ppm).

2,2'-Bis[(1,1'-biphenyl-2,2'-dioxy)phosphinyloxy]-(S)- 3,3'-di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl (B-17): colorless viscous oil; 75% yield; ^{1}H NMR (400 MHz, C_6D_6) δ 1.45 (s,18H, ^{t}Bu), 1.96 (s, 6H, Me), 2.13 (s, 6H, Me), 6.7-7.2 (m, 16H, ArH), 7.34 (s, 2H, ArH); ^{31}P NMR (162 MHz, C_6D_6) δ 141.6.

2,2'-Bis(diphenoxyphosphinyloxy)-(S)-3,3'-di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl (B-1): colorless viscous oil; 87% yield; ^{1}H NMR (400 MHz, C_6D_6) δ 1.55 (s,18H, ^{t}Bu), 1.88 (s, 6H, Me), 1.97 (s, 6H, Me), 6.6-6.8 (m, 4H, ArH), 6.8-7.1 (m, 16H, ArH), 7.20 (s, 2H, ArH); ^{31}P NMR (162 MHz, C_6D_6) δ 130.1. HRMS (FAB) calcd for $C_{48}H_{51}O_6P_2$ $[M-H]^+$ 785.3161, found 785.3158 (Δ = 0.4 ppm).

2,2'-Bis[(bis(2-naphthoxy)phosphinyloxy)]-(S)-3,3'-di-tert-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl (B-20): colorless viscous oil; 34% yield; ^{1}H NMR (400 MHz, C_6D_6) δ 1.60 (s,18H, ^{t}Bu), 1.92 (s, 6H, Me), 1.94 (s, 6H, Me), 6.9-7.6 (series of m, 28H, ArH), 7.23 (s, 2H, ArH); ^{31}P NMR (162 MHz, C6D6) δ 129.6. HRMS (FAB) calcd for $C_{64}H_{60}O_6P_2$ $[M+H]^+$ 987.3943, found 987.3939 (Δ = 0.4 ppm).

EXAMPLE 19

Synthesis of bisphosphite, B-3

To a dry THF solution (200 mL) of PCl_3 (14.23 g, 104 mmol) was added diethylamine (30.31 g, 414 mmol) in dry THF (50 mL) at 0 °C for 3 hrs under nitrogen atmosphere. Diethylamine hydrochloride was filtered off under nitorogen and the solvent

was removed from the filtrate under reduced pressure. The residue was distilled under reduced pressure to give $ClP(NEt_2)_2$ (14.14 g) in a 77.5% yield.

b.p. 90-91 deg. (4-5mmHg).

^1H NMR ($CDCl_3$) δ 1.13 (t, 12H, d = 7.2 Hz), 3.17 (m, 8H)

^{31}P NMR ($CDCl_3$) δ 158.95 ppm

To a dry THF (200 mL) solution of (S)-3,3',5,5'-tetra-t-butyl-6,6'-dimethyl-2,2'-biphenyldiol (15.83 g, 36 mmol) was added Na (3.01 g, 131 mmol) at room tenperature. The mixture was heated under reflux for 12 hrs to give disodium salt of (S)-3,3',5,5'-tetra-t-butyl-6,6'-dimethyl-2,2'-biphenyldiol. This solution was added to a dry THF (200 ml) solution of $ClP(NEt_2)_2$ (14.14 g, 80 mmol) under nitrogen at 0 °C for 30 min with well stirring. After 1 hr, desired bis-phosphoramidite (B-27) was produced in 80% yield with mono-phosphoramidite (6 %) and cyclic-phosphoramidite (A-46, 14%).

^{31}P NMR (THF solution, triphenylphosphate in C_6D_6 was used for internal standard) δ 134.81 ppm (bis-phosphoroamidite, B-27), δ 137.08 ppm (mono-phosphoroamidite), δ 138.67 ppm (cyclic-phosphoroamidite, A-46)

To this solution, 80 ml of 4N-HCl/dioxane (c.a. 290 mmol) was added from a dropping funnel. The Reaction mixture was stirred for 3hr at 0 °C, 80% of bis(dichlorophosphite) , 15% of cyclic monochlorophosphite was observed in ^{31}P NMR spectrum.

^{31}P NMR (THF solution, triphenylphosphate in C_6D_6 was used for internal standard) δ 200.03 ppm [bis(dichorophosphite)], δ 162.72 ppm (cyclic monochlorophosphite)

Diethylamine hydrochloride salt was filtered off using a glass filter under nitrogen atmosphere.

To 130 mL solution of above bis-dichlorophosphite was added a dry THF (70 mL) solution of α-naphthol (5.76 g, 40 mmol) amd triethylamine (6.0 mL, 43 mmol) at 0 °C under nitrogen. The reaction mixture was stirred for 2 hrs at 0 °C and overnight at room temperature.

^{31}P NMR (THF solution, triphenylphosphate in C_6D_6 was used for internal standard) δ 129.97 ppm (cyclic phosphite), δ 131.27 ppm (bisphosphite)

Triethylamine hydrochloride was filtered off and the filtrate was evaporated. Residual oil was dissolved in 100 mL of toluene. The toluene solution of this crude material was washed with water, $NaHCO_3$ aq., and brine. Separated organic layer was dried over anhyd. $MgSO_4$, then filtered and concentrated.

This crude material was purified by chromatography on silica gel (hexane/toluene = 5/1). Obtained colorless oil was added a small amount of acetonitrile and washed, white powders were precipitated and the precipitate was collected by filtration and dried in vacuo to give B-3 (2.50 g) in 23.3 % yield.

B-3: ^{1}H NMR ($CDCl_3$, TMS) δ 1.18 (s, 18H), 1.40 (s, 18H), 1.96 (s, 3H), 2.00 (s, 3H), 6.93 (d, 2H, J=7.32 Hz), 7.02 (t, 2H, J=7.80 Hz), 7.12 (t, 2H, J=7.96 Hz), 7.15-7.29 (m, 8H), 7.31-7.43 (m, 8H), 7.52 (s, 2H), 7.63-7.71 (m, 8H), 7.74 (d, 2H, J=8.32 Hz), 7.87 (d, 2H, J=8.36 Hz)

^{31}P NMR ($CDCl_3$) δ 158.95 ppm

EXAMPLE 20

Preparation of a chiral catalyst bearing A-43 as ligand

In a 5 ml flask, a mixture of $[Rh(COD)_2]BF_4$ (1.0 mg, 0.0025 mmol) and chiral monophosphite, A-43 (2.4 mg, 0.0050 mmol) was dissolved in 1 ml of CH_2Cl_2 under nitrogen, and the resulting solution was stirred for 10 minutes. Then, the solution was transferred to an NMR tube via syringe. ^{31}P NMR of the solution was measured at room temperature using triphenylphosphate as the standard (a solution of triphenylphosphate in C_6D_6 in a narrow tube was inserted to the NMR tube).

^{31}P NMR (101.3MHz, C_6D_6) δ 116.1 (d, J(Rh-P) = 259.9 Hz)

EXAMPLES 21-33

Asymmetric hydrogenation of dimethyl itaconate catalyzed by a rhodium complex bearing A-40

In a 10 mL glass reaction vessel with a magnetic stirring bar under nitrogen, a mixture of $[Rh(COD)_2]SbF_6$ (1.4 mg, 0.0025 mmol) and A-40 (3.0 mg, 0.0050 mmol) was dissolved in 3 mL CH_2Cl_2, and stirred at room temperature for 5 min. To this catalyst solution were added dimethyl itaconate (0.07 mL, 0.5 mmol) via syringe under nitrogen. Then, the reaction vessel was placed in a 300 mL stainless steel autoclave. The autoclave was purged with hydrogen gas and then charged with hydrogen to 100 psi (0.689 MPa). The autoclave was warmed to 50 °C and the reaction was carried out at this temperature for 20 hrs with stirring. Then, the autoclave was cooled to room temperature, and hydrogen gas was carefully released. The reaction mixture was filtered through a short pad of silica gel and the filtrate was subjected to gas chromatographic analysis using a Supelco Beta Dex 225 column. The

analysis showed quantitative conversion of dimethyl itaconate and the enantiomeric purity of dimethyl succinate, thus formed, was determined to be 97.8% ee (R). Dimethyl malate was isolated simply by removal of the solvent in vacuo.

the reactions were performed in the same manner except for the reaction temperature and the solvent used. Results are summarized in Table 1.

Table 1. Asymmetric Hydrogenation of Dimethyl Itaconate Catalyzed by Rh complexes

Example	Ligand	Solvent	Temp. (°C)	Conv. (%)	% ee
21	**A-40**	CH_2Cl_2	50	100	97.8 (*R*)
22	**A-40**	$ClCH_2CH_2Cl$	50	100	99.6 (*R*)
23	**A-22**	CH_2Cl_2	25	100	96.5 (*S*)
24	**A-24**	CH_2Cl_2	25	100	96.4 (*S*)
25	**A-35**	CH_2Cl_2	25	100	92.0 (*R*)
26	**A-34**	CH_2Cl_2	25	100	25.0 (*R*)
27	**A-42**	CH_2Cl_2	50	100	99.0 (*R*)
28	**A-42**	$ClCH_2CH_2Cl$	50	100	99.1 (*R*)
29	**A-37**	CH_2Cl_2	50	100	94.4 (*R*)
30	**A-37**	$ClCH_2CH_2Cl$	50	100	98.9 (*R*)
31	**A-38**	CH_2Cl_2	50	100	97.6 (*R*)
32	**A-38**	$ClCH_2CH_2Cl$	50	100	98.2 (*R*)
33	**A-43**	CH_2Cl_2	25	100	93.0 (*R*)

EXAMPLES 34-44

General Procedure for asymmetric hydroformylation of styrene

In a 10 mL glass reaction vessel with a magnetic stirring bar, a mixture of $Rh(acac)(CO)_2$ (1.5 mg, 0.058 mmol) and a phosphite ligand (0.232 mmol) was dissolved in benzene (0.6 mL), and stirred at room temperature for 5 min. To this solution was added styrene (1.22 g, 11.9 mmol, freshly distilled before each use) and the reaction vessel was placed in a 300 mL stainless steel autoclave. The autoclave was purged with carbon monoxide a couple of times and then charged with carbon monoxide (20 atm, 2 MPa) and hydrogen (20 atm, 2 MPa) gases. The autoclave was warmed to 60 °C and the reaction was carried out at this temperature for 24 hrs with stirring. The autoclave was cooled to room temperature, and gases were carefully released. The conversion and the branched/linear ratio were analyzed by ^1H NMR. Then, the reaction mixture was filtered through a short pad of silica gel and the filtrate was subjected to gas chromatographic analysis using a Supelco Beta

Dex-225 chiral column for the determination of enantiomeric purity of branched aldehyde product, 2-phenylpropanal. The absolute configuration of 2-phenylpropanal, thus obtained, was also determined by comparing the retention time with that of the authentically prepared (R)-2-phenylpropanal. Results are summarized in Table 2.

Table 2. Asymmetric Hydroformylation of Styren Catalyzed by Rh Complexes

Example	Ligand	Temp (°C)	Time (h)	Conv. (%)	b / l	% *ee*
34	**A-21**	60	17	100	90:10	35 (*R*)
35	**A-21**	40	17	100	90:10	43 (*R*)
36	**A-21**	30	17	30	90:10	45 (*R*)
37	**A-23**	60	17	100	94:6	39 (*R*)
38	**A-34**	40	17	12	ND	58 (*R*)
39	**A-36**	40	17	8	ND	60 (*S*)
40	**A-36**	60	17	73	92:8	55 (*S*)
41	**A-40**	60	24	100	94:6	58 (*R*)
42	**A-42**	60	24	100	94:6	30 (*R*)
43	**A-37**	60	22	100	94:6	53 (*R*)
44	**A-38**	60	22	72	95:5	48 (*S*)

EXAMPLE 45

To a 70 mL of autoclave were added the ligand (A-47, 0.0303g, 0.059 mmol), $[Rh(cod)_2(OAc)]_2$ (0.0039g, 0.007 mmol), toluene (7.6 mL), and styrene (0.420g, 4.03 mmol) under nitrogen atmosphere and the autoclave was sealed. After replacing nitrogen to OXO gas (H_2/CO = 1/1) in the autoclave, OXO gas was pressurized to 4Mpa at room temperature. The reaction was conducted at 60 °C for 3 hrs. GC analysis of the reaction mixture showed that styrene was completely consumed and 2-phenylpropanal and 3-phenylpropanal were produced in an area ratio of 26.3:1. Jones oxidation (CrO_3/H_2SO_4 aq.) of the reaction product in an acetone solution gave the corresponding carboxylic acids, respectively, with complete conversion. The absolute configulation of 2-phenylpropanoic acid obtained was R and its enantiomeric purity was found to be 70.1% ee by using chiral GC analysis.

EXAMPLE 46

To a 70 mL of autoclave were added the ligand (A-27, 0.0307g, 0.060 mmol), $[Rh(cod)_2(OAc)]_2$ (0.0039g, 0.007 mmol), toluene (7.6 mL), and styrene (0.420g, 4.03 mmol) under nitrogen atmosphere and the autoclave was sealed. After replacing nitrogen to OXO gas (H_2/CO = 1/1) in the autoclave, OXO gas was pressurized to 4Mpa at room temperature. The reaction was conducted at 60 °C for 3 hrs. GC analysis of the reaction mixture showed that styrene was completely consumed and 2-phenylpropanal and 3-phenylpropanal were produced in an area ratio of 21.4:1. Jones oxidation (CrO_3/H_2SO_4 aq.) of the reaction product in an acetone solution gave the corresponding carboxylic acids, respectively, with complete conversion. The absolute configuration of 2-phenylpropanoic acid obtained was R and its enantiomeric purity was found to be 56.3% ee by using chiral GC analysis.

EXAMPLE 47

To a 70 mL of autoclave were added the ligand (A-3, 0.0511g, 0.052 mmol), $[Rh(cod)_2(OAc)]_2$ (0.0070g, 0.013 mmol), toluene (12.0 mL), and methyl methacrylate (0.537g, 5.36 mmol) under nitrogen atmosphere and the autoclave was sealed. After replacing nitrogen to OXO gas (H_2/CO = 1/1) in the autoclave, OXO gas was pressurized to 1Mpa at room temperature. The reaction was conducted at 100 °C for 7 hrs. GC analysis of the reaction mixture showed that conversion was 43.5 % and the corresponding linear aldehyde and branch aldehyde were produced in an area ratio of 140.4:1. The enantiomeric purity of methyl 2-methyl-3-formylpropionate was 44.2% ee analyzed by chiral GC.

EXAMPLE 48

To a 70 mL autoclave were added the ligand (B-5 0.0398g, 0.045 mmol), $[Rh(cod)_2(OAc)]_2$ (0.0063g, 0.012 mmol), toluene (9.6 mL), and α-methylstyrene (0.525 g, 4.44 mmol) under nitrogen atmosphere and the autoclave was sealed. After replacing nitrogen to OXO gas (H_2/CO = 1/1) in the autoclave, OXO gas was pressurized to 0.5 Mpa at room temperature. The reaction was conducted at 60 °C for 17 hrs. GC analysis of the reaction mixture showed that conversion was 14.9 %. The products were 3-phenylbutanal and 2-phenylpropane. The enantiomeric purity of 3-phenylbutanal was 46.2% ee analyzed by chiral GC.

EXAMPLES 49-58

General procedure for the asymmetric addition of diethylzinc to cyclohexenone

In a 25 mL two-necked round bottomed flask with a magnetic stirring bar under nitrogen, a mixture of $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) and a phosphite ligand (0.02 mmol) was dissolved in dry ether (3 mL), and stirred at room temperature for 30 min. The mixture was cooled to 0 °C and to this mixture 2-cyclohexen-1-one (0.1 mL, 1 mmol) and 1.0 M diethylzinc solution in hexanes (1.5 mL, 1.5 mmol) were added dropwisely under nitrogen. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched with 1 N HCl (10 mL) and extracted with ether (10 mL x 3). Combined extracts were washed with 1 N HCl (10 mL), brine (10 mL x 2), and dried over anhydrous $MgSO_4$. ^1H NMR of crude product showed complete conversion. The enantiomeric purity of the product, 3-ethylcyclohexanone, was determined by chiral gas chromatography using a Supelco Beta Dex-225 column. The absolute configuration of the product was also determined by comparing the retention time with the authentically prepared (R)-3-ethylcyclohexanone. Results are summarized in Table 3.

Table 3. Asymmetric Addition of Diethylzinc to Cyclohexenone Catalyzed by Cu Complexes

Example	ligand	solvent	% ee
49	**B-18**	toluene	25 (*R*)
50	**B-18**	ether	30 (*R*)
51	**B-17**	toluene	36 (*R*)
52	**B-1**	toluene	36 (*R*)
53	**B-20**	toluene	15 (*R*)
54	**A-21**	toluene	23 (*S*)
55	**A-21**	ether	35 (*S*)
56	**A-34**	ether	17 (*S*)
57	**A-40**	toluene	11 (*R*)
58	**A-40**	ether	21 (*R*)

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

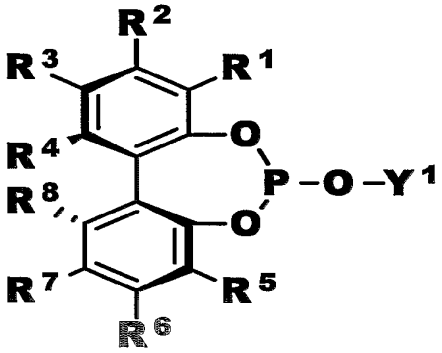
Industrial Applicability

The present invention provides efficient chiral ligands and transition metal catalysts bearing these chiral ligands, which are suitable for the production of optically active pharmaceutical and/or agrochemical products and/or their intermediates.

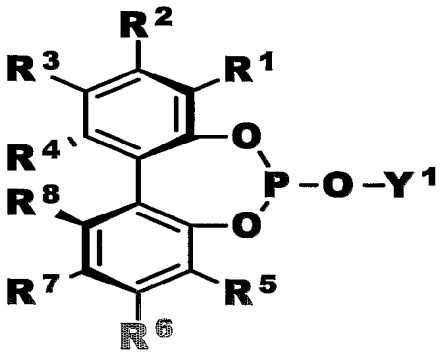
CLAIMS:

1. A novel optically active monodentate phosphite and/or phosphoramidite having an optically active biphenol moiety with axial chirality, represented by the following general formula (1):

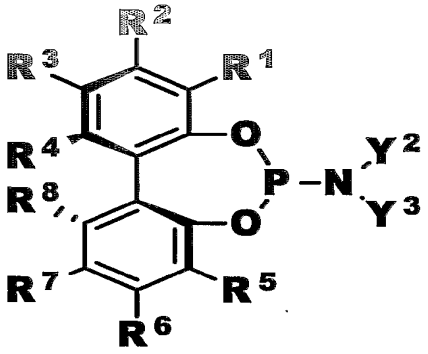
General Formula (1)



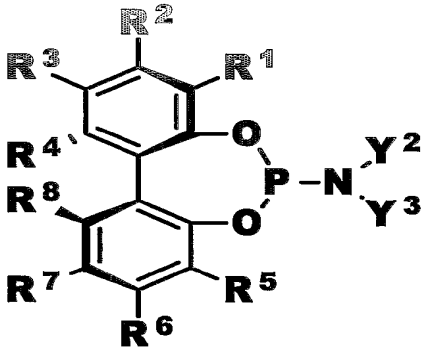
(1-1)



(1-2)



(1-3)



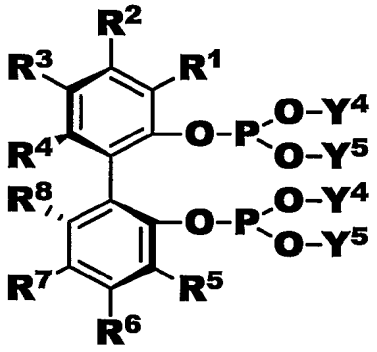
(1-4)

wherein R^1 and R^5 each represents a hydrogen atom or an optionally substituted secondary or tertiary hydrocarbon group having from 3 to 20 carbon atoms; R^2 and R^6 each represents a hydrogen atom, an optionally substituted alkyl group having from 1 to 20 carbon atoms, an optionally substituted alkoxy group having from 1 to 10 carbon atoms, an

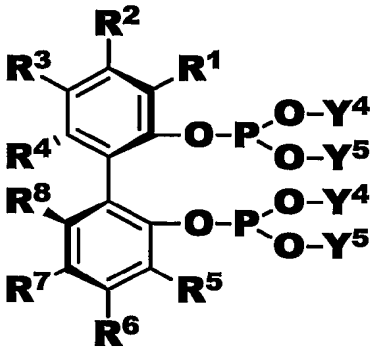
optionally substituted aryl group, or a halogen atom; R^3 and R^7 each represents an optionally substituted hydrocarbon group having from 1 to 20 carbon atoms or an optionally substituted alkoxy group having from 1 to 10 carbon atoms; R^4 and R^8 each represents a hydrocarbon atom having from 1 to 4 carbon atoms, a halogen atom, or an alkoxy group having from 1 to 4 carbon atoms; Y^1, Y^2, and Y^3 each represents an optionally substituted alkyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group; and Y^2 and Y^3 may be taken together to form a ring.

2. A novel optically active bidentate phosphite and/or phosphoramidite having an optically active biphenol moiety with axial chirality, represented by the following general formula (2):

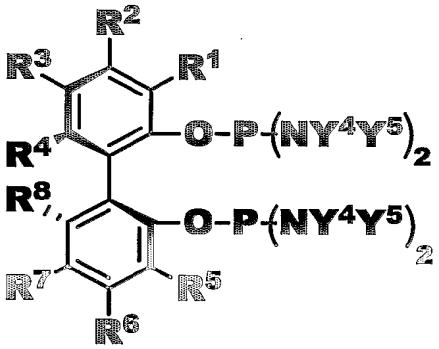
General Formula (2)



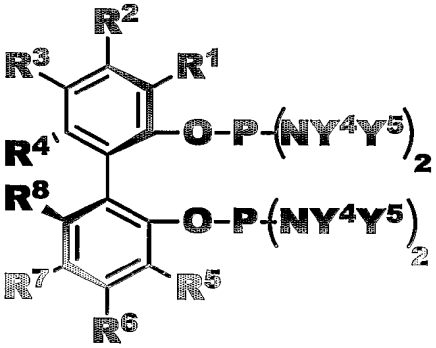
(2-1)



(2-2)



(2-3)



(2-4)

wherein R^1 and R^5 each represents a hydrogen atom or an optionally substituted secondary or tertiary hydrocarbon group having from 3 to 20 carbon atoms; R^2 and R^6 each represents a hydrogen atom, an optionally substituted alkyl group having from 1 to 20 carbon atoms, an optionally substituted alkoxy group having from 1 to 10 carbon atoms, an optionally substituted aryl group, or a halogen atom; R^3 and R^7 each represents an optionally substituted hydrocarbon group having from 1 to 20 carbon atoms or an optionally substituted alkoxy group having from 1 to 10 carbon atoms; R^4 and R^8 each represents a hydrocarbon atom having from 1 to 4 carbon atoms, a halogen atom, or an alkoxy group having from 1 to 4 carbon atoms; Y^4 and Y^5 each represents an optionally substituted alkyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group; and Y^4 and Y^5 may be

taken together to form a ring.

3. The optically active monodentate or bidentate phosphite and/or phosphoramidite according to claim 1 or 2, wherein R^4 and R^8 each represents a methyl group.

4. An optically active catalyst comprising a reaction mixture of a transition metal belonging to the groups 4 to 12 of the periodic table, or a compound thereof, and an optically active ligand, wherein the optically active ligand is the optically active monodentate phosphite and/or phosphoramidite according to claim 1.

5. An optically active catalyst comprising a reaction mixture of a transition metal belonging to the groups 4 to 12 of the periodic table, or a compound thereof, and an optically active ligand, wherein the optically active ligand is the optically active bidentate phosphite and/or phosphoramidite according to claim 2.

6. The optically active catalyst according to claim 4 or 5, wherein the transition metal belongs to the groups 8 to 12 of the periodic table.

7. A process of producing an optically active compound, which comprises the transformation of a prochiral compound in the presence of a chiral transition metal catalyst, wherein the transition metal catalyst comprises a reaction mixture of a transition metal belonging to the groups 4 to 12 of the periodic table, or a compound thereof, and an optically active ligand, wherein the optically active ligand is the optically active monodentate phosphite and/or phosphoramidite according to claim 1..

8. A process of producing an optically active compound, which comprises the transformation of a prochiral compound to an optically active compound in the presence of a chiral transition metal catalyst, wherein the transition metal catalyst comprises a reaction mixture of a transition metal belonging to the groups 4 to 12 of the periodic table, or a compound thereof, and an optically active ligand, wherein the optically active ligand is the optically active bidentate phosphite and/or phosphoramidite according to claim 2.

9. The process of producing an optically active compound according to claim 7 or 8, wherein the transition metal belongs to the groups 8 to 12 of the periodic table.

10. The process of producing an optically active compound according to claim 7 or 8, wherein R^4 and R^8 each represents a methyl group.

11. The process of producing an optically active compound according to claim 7, 8, 9, or 10, wherein the transformation of the prochiral compound is a catalytic asymmetric reaction selected from the group consisting of hydrogenation, hydroformylation, allylic substitution, hydrosilylation, and Michael addition.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/05790

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07F 7/02, 9/141, 9/06; C07C 47/00, 47/02, 49/00, 49/04, 69/00, 69/003, 69/12

US CL : 558/ 70, 73, 199, 200; 556/13, 400; 560/129, 568/ 420, 426, 429, 303, 328, 343

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 558/ 70, 73, 199, 200; 556/13, 400; 560/129, 568/ 420, 426, 429, 303, 328, 343

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,910,600 A (URATA et al) 08 June 1999 (08.06.1999) columns 95, 96 and examples.	2-11
X --- A	US 5,696,280 A (SHAPIRO, R.) 09 December 1997 (09.12.1997), columns 5-10 and examples.	2-10 --- 1
X --- A	Database CAPLUS on STN Chemical Abstracts (Columbus OHIO, USA) CA:132:166343 'Preparation of multidentate phosphites'. WADA et al. JP 2000053688, 22 February 2000.	2-3 --- 1
X --- A	US 5,952,530 A (ARGYROPOULOS et al) 14 September 1999 14.09.1999 especially columns 27-34.	2-6 --- 1
X	Database CAPLUS on STN Chemical Abstracts (Columbus OHIO USA) CA:134:252470 'Multidentate phosphite ligands , catalytic compositions utilixing such catalytic compositions'. BOYLES et al. WO 2001/021580, 29 March 2001.	2-6

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

03 July 2003 (03.07.2003)

Date of mailing of the international search report

13 AUG 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

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Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

PCT/US03/05790

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	Database CAPLUS on STN Chemical abstracts (Columbus OHIO USA) CA:136:401880 Orthosubstituted chiral phosphines and phosphinites and their use in asymmetric catalytic reactions'. ZHANG, X. WO 2002/040491 23 May 2002.	2-11 ---------- 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/05790

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1, 3 (in part), drawn to a compound of the formula 1-1 or 1-2 which is a mono phosphite compound wherein the phosphorus is part of a ring system.

Group II, claim(s) 1, 3 (in part), drawn to a compound of the formula 1-3 or 1-4 which is ca mono phosphoramide compound wherein the phosphorus is part of a ring system.

Group III, claim(s) 2 (in part), drawn to a compound of formula 2-1 or 2-2 which is a bis phosphite compound (two phosphorus atoms) .

Group IV, claim(s) 2(in part), drawn to drawn to a compound of formula 2-3 or 2-4 which is a bis phosphoramide (two phosphorus atoms) .

Group V, claim(s) 4, 6, 7, 9, 10 and 11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-1 or 1-2 and a method of using the catalyst to form a compound through hydrogenation .

Group VI, claim(s) 4,6,7, 9,10 and 11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-3 or 1-4 and a method of using the catalyst to form a compound through hydrogenation .

Group VII, claim(s) 5, 6, 8, and 9-11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-1 or 2-2 and a method of using the catalyst to form a compound through hydrogenation .

Group VIII, claim(s) 5, 6, 8, and 9-11 (in part) drawn to transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-3 or 2-4 and a method of using the catalyst to form a compound through hydrogenation .

Group IX, claim(s) 4, 6, 9, 10 and 11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-1 or 1-2 and a method of using the catalyst to form a compound through hydroformylation .

Group X, claim(s) 4,6,7, 9,10 and 11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-3 or 1-4 and a method of using the catalyst to form a compound through hydroformylation .

Group XI, claim(s) 5, 6, 8, and 9-11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-1 or 2-2 and a method of using the catalyst to form a compound through hydroformylation.

Group XII, claim(s) 5, 6, 8, and 9-11 (in part) drawn to transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-3 or 2-4 and a method of using the catalyst to form a compound through hydroformylation .

Group XIII, claim(s) 4, 6, 9, 10 and 11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-1 or 1-2 and a method of using the catalyst to form a compound through allylic substitution.

Group XIV, claim(s) 4,6,7, 9,10 and 11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-3 or 1-4 and a method of using the catalyst to form a compound through allylic substitution.

Group XV, claim(s) 5, 6, 8, and 9-11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-1 or 2-2 and a method of using the catalyst to form a compound through allyllic substitution.

Group XVI, claim(s) 5, 6, 8, and 9-11 (in part) drawn to transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-3 or 2-4 and a method of using the catalyst to form a compound through allylic substitution.

Group XVII, claim(s) 4, 6, 9, 10 and 11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-1 or 1-2 and a method of using the catalyst to form a compound through hydrosilylation.

Group XVIII, claim(s) 4,6,7, 9,10 and 11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-3 or 1-4 and a method of using the catalyst to form a compound through hydrosilylation.

Group XIX, claim(s) 5, 6, 8, and 9-11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-1 or 2-2 and a method of using the catalyst to form a compound through hydrosilylation.

Group XX, claim(s) 5, 6, 8, and 9-11 (in part) drawn to transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-3 or 2-4 and a method of using the catalyst to form a compound through hydrosilylation.

Group XXI, claim(s) 4, 6, 9, 10 and 11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-1 or 1-2 and a method of using the catalyst to form a compound through Michael addition.

Group XXII, claim(s) 4,6,7, 9,10 and 11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-3 or 1-4 and a method of using the catalyst to form a compound through Michael addition.

Group XXIII, claim(s) 5, 6, 8, and 9-11 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-1 or 2-2 and a method of using the catalyst to form a compound through Michael addition.

Group XXIV, claim(s) 5, 6, 8, and 9-11 (in part) drawn to transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-3 or 2-4 and a method of using the catalyst to form a compound through Michael addition.

Group XXV, claim(s) 4, 6, 9, and 10 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-1 or 1-2 and a method of using the catalyst to form a compound through a reaction that is not given in claim 11. If this group is chosen a specific reaction must be chosen.

Group XXVI, claim(s) 4,6,7, 9, and 10 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 1-3 or 1-4 and a method of using the catalyst to form a compound through a reaction that is not given in claim 11. If this group is chosen a specific reaction must be chosen.

Group XXVII, claim(s) 5, 6, 8, and 9-10 (in part), drawn to a transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-1 or 2-2 and a method of using the catalyst to form a compound through a reaction that is not given in claim 11. If this group is chosen a specific reaction must be chosen.

Group XXVIII, claim(s) 5, 6, 8, and 9-10 (in part) drawn to transition metal catalyst from transition metal groups 4-12 with a ligand attached to a compound of formula 2-3 or 2-4 and a method of using the catalyst to form a compound through a reaction that is not given in claim 11. If this group is chosen a specific reaction must be chosen.

The inventions listed as Groups I-XXVIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is a mono phosphite moiety which has only one phosphorus and is surrounded by 3 oxygens in a ring system which has chemical and physical properties that are determined by the phosphorus ring and the three oxygens attached thereto. Group II has is a monophosphoramide which has one phosphorus , two oxygens and one nitrogen attached to the phosphorus in a ring system. The nitrogen give the ring structure of being a phosphoramide which has very different chemical and physical properties than the monophosphite. Group III is a

bis phosphite which contains two phosphorus atoms which are not linked to each other in a ring system. This is chemically and physically different from the monophosphite which has only one phosphorus that is part of a ring system which includes the diphenyl group. The structure in Group III is also different from the ring structure in Group II that the compounds in Group II are phosphoramides and not a bis phosphite. Group IV is drawn to a bis phosphoramide which is not phosphite and does not have only one phosphorus in a ring structure which includes the biphenyl moiety.

Group V is drawn to a transition metal catalyst and a method using the transition metal catalyst in a process of hydroformylation. This group has already been grouped by a compound and a method of use . The compounds in group are used as catalysts. The compounds in Group I-IV, in themselves, cannot be used as catalysts. The compounds in Groups I-IV can be used as extractants for extracting metals from solutions. This cannot be performed by Groups V-XXVIII which have a transition metal as part of the compound and therefore have no lone pairs left on the phosphorus to extract metals. Also there is no unity of invention in Groups V-XXVIII and Groups I-IV. Unity of invention is present when there is a compound , and a method of use of that compound, and/or a method of making that compound and/or an apparatus especially designed for the method of preparing the compound. Groups I-IV are compounds and they cannot be used by themselves as a catalyst for the process of making optically active compounds. Groups V-XXVIII have a special technical feature in each group in that they are drawn to different compounds which are catalysts and contain a metal and those different compounds can be used for a method of say -hydrogenation. The different groups of catalysts again are drawn to those which have different chemical and physical characteristics by their structure. The examiner could have also broken up the catalysts by the metal components since a titanium catalyst is different from a palladium catalyst both structurally and chemically but the examiner has left them in one group as a courtesy. The groups have been again divide into different groups depending on the method of use since the method of use groups have no unity of invention . Unity of invention is present if there is a compound and a method for using the compound. Or a group of similar method example a method for using a compound as a surfactant and as an ingredient in a shampoo which is also the surfactant portion of the shampoo. These different methods of use would fall under a method since they are closely related in that their function is a surfactant. However hydrogenation, hydrosilylation, allylic substitution etc are methods which are not closely related. The reagents are different in the method for hydrogenation than for hydrosilyation etc. There is no need for a silyl group in a hydrogenation reaction. Nor is there need for an allylic position to be present for a hydrosilyation or hydrogenation etc. There is no unity of invention in taking various compounds and using various different reagents and conditions to form various different products. The requirement for lack of unity is that there be a special technical feature and unity of invention. If they are not both present then there is a lack of unity. There may be a special technical feature between each of the reagents as catalysts (i.e. metal monophosphite) and the method of using the phosphite as in a hydrogenation reaction. However the reactions themselves do not fall under the unity of invention and therefore have been separated into the appropriate groups.

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE, EAST, BEILSTEIN

search terms: structure searches on each compound, chiral, amide, phosphite, hydroformylation, Michael addition, hydrogenation